Clinical applications of transient elastography

Kyu Sik Jung¹,³ and Seung Up Kim¹,³

¹Department of Internal Medicine, and ²Institute of Gastroenterology, Yonsei University College of Medicine, Seoul; ³Liver Cirrhosis Clinical Research Center, Seoul, Korea

Chronic liver disease represents a major public health problem, accounting for significant morbidity and mortality worldwide. As prognosis and management depend mainly on the amount and progression of liver fibrosis, accurate quantification of liver fibrosis is essential for therapeutic decision-making and follow-up of chronic liver diseases. Even though liver biopsy is the gold standard for evaluation of liver fibrosis, non-invasive methods that could substitute for invasive procedures have been investigated during past decades. Transient elastography (TE, FibroScan®) is a novel non-invasive method for assessment of liver fibrosis with chronic liver disease. TE can be performed in the outpatient clinic with immediate results and excellent reproducibility. Its diagnostic accuracy for assessment of liver fibrosis has been demonstrated in patients with chronic viral hepatitis; as a result, unnecessary liver biopsy could be avoided in some patients. Moreover, due to its excellent patient acceptance, TE could be used for monitoring disease progression or predicting development of liver-related complications. This review aims at discussing the usefulness of TE in clinical practice. (Clin Mol Hepatol 2012;18:163-173)

Keywords: Chronic liver disease; Cirrhosis; Decompensation; Fibroscan; Fibrosis; Hepatocellular carcinoma; Liver stiffness measurement; Transient elastography

INTRODUCTION

As liver fibrosis is closely related to the prognosis of patients with chronic liver diseases (CLD), assessment of the extent and progression of liver fibrosis is important in deciding treatment strategies for patients with CLD.¹² Although liver biopsy (LB) has been considered as the golden standard for evaluation of liver fibrosis to date, several issues such as sampling errors, intra- and inter-observer variability, and potential life-threatening complications have prevented wide use of LB in clinical practice.³⁴ Moreover, serial LB examinations to monitor the dynamic changes in liver fibrosis or disease progression is impossible because of the inherent invasiveness. Therefore, the need for a non-invasive method of liver fibrosis assessment has increased and various surrogate models using blood or clinical parameters have been proposed.⁵

Recently, liver stiffness measurement using transient elastography (TE; FibroScan®, EchoSens, Paris, France), which is an ultrasound-based modality for quantitative assessment of liver fibrosis, has been introduced and had gained increasing attention globally. First reported in 2003, its clinical usefulness has been investigated in a large number of studies.⁶-¹³ Most studies have demonstrated diagnostic accuracy of TE for assessing liver fibrosis in various etiology of CLDs cross-sectionally.¹⁴-¹⁶ Recently, an additional role of

Abbreviations:
ALT, alanine aminotransferase; APRI, aspartate aminotransferase-to-platelet ratio index; ASPRI, age-spleen-platelet ratio index; AST, aspartate aminotransferase; AUROC, areas under the receiver operating characteristics curve; BMI, body mass index; CHB, chronic hepatitis B; CHC, chronic hepatitis C; CLD, chronic liver disease; HCC, hepatocellular carcinoma; HEV, high risk esophageal varices; HVPG, hepatic venous pressure gradient; IQR, the interquartile range; IQR/M, the interquartile range/median value; kPa, kilopascals; LB, liver biopsy; LRE, liver related events; LSPS, LSM spleen diameter to platelet ratio score; TE, transient elastography

Corresponding author: Seung Up Kim
Department of Internal Medicine, Yonsei University College of Medicine, 250 Seongsan-ro, Seodaemun-gu, Seoul 120-752, Korea
Tel: +82-2-2228-1982, Fax: +82-2-393-6884, E-mail: ksukorea@yuhs.ac

Received: May 15, 2012
Accepted: May 21, 2012

Copyright © 2012 by The Korean Association for the Study of the Liver
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/3.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.
TE, monitoring disease progression has begun to attract attention, which indicates that the role of TE is not merely limited in lessening unnecessary LB, but TE can enable establishment of tailored management strategies by providing more detailed prognostic information.17

Here, we review currently available data regarding the role of TE in liver fibrosis assessment and prognosis prediction.

TRANSIENT ELASTOGRAPHY

The basic principle of TE is that the propagation velocity of a wave through a homogenous tissue is proportional to its elasticity, which is correlated with the amount of fibrosis in the liver.18 Briefly, TE consists of an ultrasound transducer mounted on the axis of the vibrator, which produces vibration of a mild amplitude and low frequency (50 Hz), consequently inducing an elastic shear wave that propagates through the liver. Pulse-echo ultrasound follows the propagation of the shear wave and measures its velocity, which is related to liver tissue stiffness. It is reported that the velocity of elastic waves is faster in fibrotic liver than normal livers in previous study.6

Performance of TE takes only a few minutes, and it is well tolerated by most patients. TE is performed on the right lobe of the liver, through intercostal spaces, with the patient lying in dorsal decubitus with the right arm in maximal abduction. The operator, assisted by time motion ultrasound images, locates the probe in a liver portion at least 6 cm thick and free of large vascular structures and gallbladders and presses the probe button to commence the measurement. Usually, 10 valid measurements should be performed to examine a patient with TE. The median value of the ten valid measurements is considered representative of liver elasticity. The success rate is calculated as the number of valid measurements divided by the total number of measurements. Examinations with a success rate higher than 60% are considered reliable. The results are immediately obtained after performance of TE and expressed in kilopascals (kPa), corresponding to the median value of 10 validated measurements (range 2.5-75 kPa). The interquartile range (IQR), which represents the intrinsic variability of TE, <30% of the median indicates a high-quality result.

However, in a recent study, the IQR/median value (IQR/M) was recently proposed as a factor that determines the accuracy of TE irrespective of the success rate, in patients with chronic hepatitis C (CHC).19 In contrast, regarding patients with chronic hepatitis B (CHB), advanced liver fibrosis stage on LB (F3-4) was significantly associated with non-discordance with LB data, regardless of IQR/M and success rate.20 Thus, further studies are necessary to resolve this controversial issue.

NORMAL TE VALUES

Besides assessment of liver fibrosis, it is also important to confirm whether TE can reliably identify patients with CLD in the normal population. Nevertheless, only few studies have been available. Roulot et al examined a large cohort of 429 apparently healthy French subjects to establish normal TE values (5.81±1.54 [range, 3.8-8.0] kPa in men vs. 5.23±1.59 [range, 3.3-7.8] kPa in women, P<0.01).21 Normal TE values for Asian subjects have been also reported. Fung et al reported a mean TE value in 28 healthy living-related liver donors of 4.6 (range, 2.0-7.1) kPa, and all subjects had TE values of <7.2 kPa, which indicated that they had no significant fibrosis.22 Our group has also reported that the normal range of TE values is 3.9-5.3 kPa, which was calculated from 69 strictly selected living liver and kidney donors.23 All these data demonstrated that TE can reliably identify high-risk subpopulations without overlap between the normal and abnormal ranges of TE values and indicated that the use of TE can be extended as a screening tool.24

However, it is also noticeable that the mean LS values in Asian studies seem to be slightly lower than those in European studies; furthermore, the influence of gender and metabolic syndrome on TE value remains controversial.25 Thus, further large-scale confirmative studies are still required.

DIAGNOSTIC PERFORMANCE OF ASSESSING LIVER FIBROSIS

Most studies on TE have focused on its ability to identify significant fibrosis and cirrhosis, because the presence of significant fibrosis is an indication for antiviral treatment and the presence of cirrhosis is cornerstone for initiating surveillance program for the early detection of hepatocellular carcinoma (HCC) development. As the current gold standard for liver fibrosis assessment, LB is the reference for calculation of the diagnostic accuracy of TE. The accuracy of TE has been estimated by calculating areas under the receiver operating characteristics curve (AUROC) for prediction of each fibrosis stage based on LB and comparing these with the AUROC values of other non-invasive models.
**Hepatitis C**

A considerable number of studies from Western nations have demonstrated that TE values are significantly correlated with histological fibrosis stage and have high diagnostic accuracy superior or similar to other non-invasive methods such as FibroTest in patients with CHC (Table 1).\textsuperscript{14-16,30-33} In these studies, the AUROC of TE ranged from 0.77 to 0.90, with a cutoff value of 6.2-8.7 kPa for assessment of significant fibrosis (F≥2), and an AUROC of 0.90-0.97 and cutoff value of 9.6-14.8 kPa for assessment of cirrhosis (Table 1). In South Korea, one multi-center cohort study reported the diagnostic performance of TE in populations with CHC (Table 1).\textsuperscript{29} In this study, the optimal cutoff value for significant fibrosis was 6.2 kPa and that for cirrhosis was 11.0 kPa, which were more accurate than other non-invasive parameters such as aspartate aminotransferase (AST)-to-platelet ratio index (APRI).\textsuperscript{29}

**Hepatitis B**

Marcellin et al first reported the diagnostic accuracy of TE in populations with CHB.\textsuperscript{14} In this study, the AUROC was 0.81 for significant fibrosis and 0.93 for cirrhosis. Several other studies have also reported the diagnostic accuracy of TE in patients with CHB (Table 1).\textsuperscript{14-16,30-33} The performance and corresponding cutoff TE values for predicting significant fibrosis (AUROC, 0.81-0.95; cutoff value, 6.3-7.9 kPa)\textsuperscript{32,16} and cirrhosis (AUROC, 0.80 to 0.98; cutoff value, 9-13.8 kPa) are shown in Table 1.\textsuperscript{14-16,30-33} Currently, TE is considered to have an acceptable diagnostic accuracy in patients with CHB,\textsuperscript{14} although the overall AUROCs seem slightly lower than those reported from populations with CHC (Table 1).

In general, the cutoff values for cirrhosis in patients with CHB tend to be lower than those for CHC. This phenomenon can be explained by the fact that the amount of liver fibrosis is lower because hepatitis B virus tends to generate macronodular cirrhosis. In addition, the physician should also keep in mind the overestimating influence of alanine aminotransferase (ALT) flare, which is frequent in CHB.\textsuperscript{35} Thus, TE values in populations with CHB should be interpreted cautiously due to the simultaneous possibility of false negatives (low fibrotic extent) and false positives (high ALT).

To overcome the confounding effect of high ALT, several studies have suggested varying cutoff values according to ALT levels in patients with CHB.\textsuperscript{32,16}

**Other etiologies**

Other studies have reported the accuracy of TE in patients with CLD related to etiologies other than CHB and CHC.\textsuperscript{16-46} First, the role of TE was investigated in patients with hepatitis C and HIV co-infection.\textsuperscript{36,40-42} In these studies, the AUROC of TE for significant fibrosis ranged from 0.72 to 0.87, with cutoff values of 4.5-9.3 kPa, and the AUROC for cirrhosis from 0.87 to 0.99, with cutoff values of 11.8-14.0 kPa, which are similar to those in

Table 1. Diagnostic performance of transient elastography in predicting significant fibrosis (≥F2) and cirrhosis (F4) in patients with chronic hepatitis C and B

| Authors          | Etiology | Country | Patients | ≥F2 (%) | F4 (%) | Cut-offs (kPa) ≥F2/F4 | AUROC ≥F2/F4 | Se (%) | Sp (%) | +LR | -LR |
|------------------|----------|---------|----------|---------|--------|-----------------------|--------------|--------|--------|-----|-----|
| Castera et al (2005) | HCV      | France  | 183      | 74      | 25     | 7.1-12.5              | 0.83/0.95    | 67/97  | 89/91  | 6.09/9.66 | 0.37/0.14 |
| Ziol et al (2005)   | HCV      | France  | 251      | 65      | 19     | 8.7-14.5              | 0.79/0.97    | 56/86  | 91/96  | 6.63/23.05 | 0.48/0.14 |
| Arena et al (2008)  | HCV      | Italy   | 150      | 56      | 19     | 7.8-14.8              | 0.91/0.98    | 83/94  | 82/92  | 4.58/11.27 | 0.20/0.07 |
| Nitta et al (2009)  | HCV      | Japan   | 165      | 60      | 14     | 7.1-9.6               | 0.88/0.90    | 80/91  | 80/78  | 4.1/- | 4.2/-|
| Siril et al (2010)  | HCV      | Romania | 150      | 89      | 10     | 6.8-13.3              | 0.77/0.97    | 60/93  | 73/96  | 3.53/24.08 | 0.64/0.07 |
| Kim et al (2011)    | HCV      | Korea   | 91       | 55      | 9      | 6.2-11.0              | 0.90/0.97    | 76/77  | 97/93  | 30.4/0.3 | 12.8/0.2  |
| Marcellin et al (2009) | HBV    | France  | 173      | 50      | 8      | 7.2-11.0              | 0.81/0.93    | 70/98  | 83/75  | 4/1/- | -0.01 |
| Kim et al (2009)    | HBV      | Korea   | 91       | 90      | 42     | -/9                  | -/0.80       | -/82   | -/-   | -/-   | -/-   |
| Chan et al (2009)   | HBV      | China   | 161      | 77      | 24     | -/9                  | -/0.93       | -/98   | -/75   | -/-   | -/-   |
| Kim et al (2009)    | HBV      | Korea   | 130      | 92      | 67     | -/10.1               | -/0.84       | -/76   | -/81   | -/-   | -/-   |
| Zhu et al (2010)    | HBV      | China   | 175      | 45      | 16     | 7.9-13.8             | 0.95/0.98    | 88/93  | 90/91  | -/-   | -/-   |
| Ogawa et al (2011)  | HBV      | Japan   | 44       | 45      | 9      | 6.3-12.0             | 0.86/0.89    | 95/75  | 74/88  | 3.66/- | 6.58/- |

AUROC, area under the receiver operating characteristic curve; HCV, hepatitis C virus; HBV, hepatitis B virus; Se, sensitivity; Sp, specificity; +LR, positive likelihood ratio; -LR, negative likelihood ratio.
patients with CHC only. Additionally, recent studies have investigated the usefulness of TE in patients with non-viral liver disease such as primary biliary cirrhosis, primary sclerosing cholangitis, or Wilson’s disease.\textsuperscript{37,38,43,44} Although the diagnostic accuracy was considerable (AUROC, range 0.81-0.95 for significant fibrosis and 0.91-0.96 for cirrhosis), its usefulness requires further validation. Interestingly, recent studies have suggested the ability of TE to assess fibrosis stage in patients taking methotrexate with potential hepatotoxicity due to rheumatoid arthritis, inflammatory bowel disease, or psoriasis.\textsuperscript{39,45,46}

Meta-analysis

Four meta-analyses have assessed the diagnostic performance of TE.\textsuperscript{47-50} In the most large-scaled study including 50 studies, the mean AUROCs for the diagnosis of significant fibrosis and cirrhosis were 0.84 and 0.94, respectively, with optimal cutoff values of 7.6 and 13.01 kPa, respectively.\textsuperscript{48} Although previous meta-analyses suggested that TE is a reliable method for assessment of liver fibrosis stage irrespective of etiology, it should be noted that most studies included in the meta-analysis was based on Western populations with CHC. Consequently, it would be unwise to apply these cutoff values from previous meta-analysis to patients with diverse CLD etiologies.

Combination with other fibrosis prediction models

To increase the accuracy of liver fibrosis assessment, new approaches using a combination of TE and other fibrosis prediction models have been proposed in several studies.\textsuperscript{51-56} A recent study by Castera et al suggested that the number of LB for assessment of significant fibrosis could be significantly reduced through the use of combinations of TE and FibroTest in populations with CHC.\textsuperscript{51} Similarly, our group also demonstrated that the performance of TE can be enhanced when combined with other fibrosis prediction models such as FibroTest in patients with CHB.\textsuperscript{54-56} However, the cost-effectiveness of combining other non-invasive models with TE needs to be clarified in the future.

changes in TE values during antiviral treatment

Due to the ease, safety, and rapidity of performing, it can be assumed that TE can be used for monitoring of the dynamic changes of liver fibrosis during anti-viral or anti-fibrotic treatment. Indeed, several studies have reported the clinical usefulness of TE for monitoring of the potential fibrosis regression during antiviral treatment in patients with CHC and CHB.\textsuperscript{33,57,58}

Hepatitis C

The clinical implications of changes in TE values during antiviral treatment for patients with CHC have been investigated in several studies. Two prospective studies by Vergniol et al\textsuperscript{57} and Ogawa et al\textsuperscript{58} demonstrated that patients with CHC showing sustained virological responses to pegylated interferon-ribavirin combination therapy had significantly reduced TE values at the end of follow-up. Moreover, Ogawa et al reported that patients with non-sustained virological responses but with a biochemical response showed a greater reduction in TE values than those with a non-biochemical response.\textsuperscript{58} Subsequent studies reported similar results, suggesting that changes in TE values during antiviral treatment in patients with CHC may represent alterations in liver fibrosis severity.\textsuperscript{59,60} However, it was not clearly indicated in these studies whether the reduction in TE values was closely correlated with regression of liver fibrosis based on paired biopsy and with favorable long-term clinical outcomes.

Hepatitis B

Dynamic changes in TE values during antiviral treatment in patients with CHB have been mostly reported in Asian countries.\textsuperscript{30,61-63} In a large prospective cohort study of 426 patients, Fung et al reported that a significant decline in TE value occurred in patients with CHB after 3 years of antiviral treatment using oral agents.\textsuperscript{61} However, the significant reduction in TE values at follow-up compared with baseline (6.1 kPa vs. 7.8 kPa respectively) was limited in patients who had elevated ALT levels at baseline and subsequent normalization after 3 years. As liver histology was not available in this study, it was not certain that decline in TE values reflected liver fibrosis regression or ALT stabilization of by antiviral treatment. To exclude the confounding effect of high ALT, our group investigated changes in TE values during antiviral treatment in 41 patients with CHB showing low ALT levels (≤2× upper limit of normal).\textsuperscript{30} After 1-2 years of antiviral treatment, TE values significantly decreased compared with baseline, whereas ALT levels were unchanged (Fig. 1). Interestingly, 3 patients with reduced TE values experienced concomitant fibrosis regression on follow-up.
biopsy, suggesting the potential fibrosis regression by long-term antiviral treatment can be monitored using TE.

However, whether changes in TE values indicate fibrosis regression remains controversial, because a recent study by Lim et al, which compared serial TE values and paired LB in 15 patients with CHB undergoing antiviral treatment, reported that the reduction in TE values was correlated with improved necroinflammatory scores, not with fibrosis regression.\(^{62}\)

PREDICTION OF HEPATIC DECOMPENSATION

Foucher et al\(^{64}\) reported that the cutoff value of 27.5, 37.5, 49.1, 53.7, and 62.7 kPa had >90% negative predictive values for the presence of large esophageal varices (stage 2/3), Child-Pugh score B or C, past history of ascites, HCC, and esophageal bleeding, respectively. Subsequently, correlations between TE values and hepatic decompensation due to increased portal hypertension have been investigated in several studies.

A significant correlation between TE values and portal hypertension, expressed as the hepatic venous pressure gradient (HVPG), was demonstrated by Vizzutti et al,\(^{65}\) suggesting that TE may reflect a progressive rise in portal pressure mainly due to increased hepatic vascular resistance caused by fibrillar extracellular matrix accumulation. As variceal bleeding is the most important complication of portal hypertension, the relationship between TE values and the presence of esophageal varices has been also investigated.

Figure 1. Changes in TE values and ALT levels between pre-and post antiviral treatment in patients with CHB who underwent follow-up TE after 1 year (n=23, A) or 2 years (n=18, B) of antiviral treatment using nucleoside analogs. In both groups, TE values decreased significantly after antiviral treatment, whereas ALT levels were unchanged. TE, transient elastography; ALT, alanine aminotransferase (adapted from reference 30).

Figure 2. Cumulative incidence rates of EV bleeding based on LSPS values. The incidence of variceal bleeding increased significantly in association with higher LSPS value (long-rank test, \(P<0.001\); A) Among patients with high-risk EV, the incidence rate of variceal bleeding was significantly higher in patient with LSPS \(>6.5\) (subgroup 2; B) than those with LSPS \(<6.5\) (subgroup 1; B). EV, esophageal varice; LSPS, liver stiffness-spleen diameter to platelet ratio score (adapted from reference 70).
in several studies.\textsuperscript{66-68} All of these studies demonstrated that there is a significant correlations between TE values and the presence of esophageal varices and that TE values could predict the presence of large varices (more than grade 2).\textsuperscript{66,67} Although TE can predict the presence of esophageal varices and consequently assist in selection of candidates for endoscopic screening or prophylactic treatment, several issues still remain unresolved. First, the cutoff values (range, 13.9-21.5 kPa) and performance of TE were varied among the studies (AUROC range, 0.76-0.85).\textsuperscript{66-68} Second, TE alone seems insufficient to predict the presence of esophageal varices.

To achieve more high accuracy, Kim et al recently proposed a novel prediction model (liver stiffness-spleen diameter to platelet ratio score [LSPS]) using TE values and other parameters that reflect portal hypertension as constituent variables in patients with CHB.\textsuperscript{69} Overall, this model had excellent diagnostic accuracy for prediction of high risk esophageal varices (HEV, AUROC=0.953; negative predictive value 94.7%, positive predictive value 93.3%). Beyond this cross-sectional analysis, a subsequent study by same group recently reported that LSPS can be a reliable predictor of the development of variceal bleeding.\textsuperscript{70} In this prospective, longitudinal study of 577 patients with CHB, those with LSPS ≥5.5 had higher cumulative incidence rates of esophageal variceal bleeding during the follow-up period and LSPS score ≥6.5 was an independent risk factor of variceal bleeding from HEV, indicating that prophylactic treatment should be considered in these high risk patients (Fig. 2).

**PREDICTION OF HCC DEVELOPMENT**

Given that advanced liver fibrosis and cirrhosis are the most important risk factors of HCC development, several Asian studies have investigated the clinical role of TE for predicting HCC development.\textsuperscript{71-73} The first large prospective study of 866 Japanese patients with CHC was conducted to investigate whether TE could predict the risk of HCC development.\textsuperscript{71} In this study, TE value was selected as one of independent risk factors for HCC development, and patients with higher TE values had a significantly higher risk of HCC development, with a hazard ratio of 16.7 with 10.1-15 kPa, 20.9 with 15.1-20 kPa, 25.6 with 20.1-25 kPa, 45.5 with over 25 kPa, as compared to under 10 kPa (Fig. 3A). Similarly, in populations with CHB, the similar role of TE was confirmed in large cohort study of 1,130 Korean patients with CHB.\textsuperscript{72} In this study, stratified TE value was also identified as an independent risk factor for HCC development, with relative risks of 3.07, 4.68, 5.55, and 6.60 for respective TE values of 8-13 kPa, 13-18 kPa, 18-23 kPa, and >23 kPa compared TE value to under 8 kPa (Fig. 3B). Interestingly, when patients with available follow-up TE values were analyzed, the risk of HCC development can be changed according to the pattern of the changes in TE values, which proposed the potential role for TE as a dynamic monitoring tool for risk estimation of HCC development. In addition, another prospective study by Fung et al also demonstrated the usefulness of TE for prediction of HCC development in patients with 528 HBeAg-negative CHB.\textsuperscript{73} Although the performance of TE and a TE based model (LSPS)
for prediction of HCC was superior to other non-invasive fibrosis prediction models, such as APRI, age-spleen-platelet ratio index (ASPRI), P2/MS, and FIB-4, the role of TE in this setting need to be validated in other ethnicities.

Lastly, a recent study by Kim et al reported that the TE could predict the development of liver-related event (LREs) including hepatic decompensation and HCC development in patients with CHB with histologically advanced liver fibrosis (≥F3). TE values was selected as independent predictor of LRE development and patients with a TE value >19 kPa were at significantly greater risk than those with a TE value ≤19 kPa.

**USEFULNESS OF TE IN SURGICAL SETTING**

Because, TE values show significant correlations with portal hypertension and HCC development, prediction of postoperative short term outcomes such as hepatic insufficiency and long-term outcomes such as recurrence or liver-related death using TE has been tested in several pilot studies. If further studies validate these results, TE will facilitate stratification of patients according to different prognosis assessed using TE values.

**Postoperative hepatic insufficiency**

Recently, our group has investigated whether preoperative TE values could predict the development of postoperative hepatic insufficiency after curative resection of HCC. In this study, multivariate analysis revealed that TE values >25.6 kPa was identified as the only predictor of postoperative insufficiency. The AUROC of 25.6 kPa was higher than that of ICG R15 (0.824 vs. 0.620, respectively). Similar results were obtained in a subsequent investigation by our group. In this study, the performance of TE was superior to that of diffusion-weighted MRI, which has also been known as a noninvasive fibrosis prediction tool, for assessment of liver fibrosis and prediction of postoperative hepatic insufficiency.

**HCC recurrence after curative resection**

Our group also investigated whether preoperative TE could predict recurrence after curative resection of HCC, based on the assumption that the severity of liver fibrosis assessed using TE is correlated with de novo recurrence of HCC. In an analysis of 133 patients who underwent preoperative TE and curative resection (HCC recurred in 62 patients), TE was selected as an independent predictor of recurrence, whereas the histological fibrosis status was not. In the study, patient with preoperative TE values >13.4 kPa were at greater risk for recurrence with a hazard ratio of 1.925 (P=0.010, Fig. 4). More specifically, when recurrence was stratified into early (<2 year) and late (≥2 year) recurrence, TE values were significantly related to late recurrence. These results suggest that preoperative TE could reveal the potential influence of liver fibrosis on recurrence and explain multicentric carcinogenesis from a fibrotic liver. However, more data are needed to clarify this issue.

**Recurrence of hepatitis C after transplantation**

Several studies have suggested that TE could predict fibrosis progression in patients with recurrent hepatitis C after liver transplantation. Initial study by Carrión et al reported that an AUROC was 0.90 for significant fibrosis and 0.98 for cirrhosis in 124 liver transplant recipients with recurrent hepatitis C infection. Using a cutoff value of 8.5 kPa, the sensitivity, specificity, negative predictive value, and positive predictive value for diagnosis of significant liver fibrosis were 90%, 81%, 79%, and 92%, respectively. Similar results were reported in several subsequent studies. In addition, Rigamonti et al showed that TE values changed in parallel with fibrosis staging in patients with paired LB during the post-liver transplantation follow-up period.
LIMITATIONS AND FAILURE

Although TE has revealed excellent diagnostic accuracy with excellent inter-observer and intra-observer agreement, there are some confounding factors which influence the results of TE. At first, the extent of necroinflammatory activity has been known to influence TE results in patients with viral hepatitis, resulting in an overestimation of TE values that increases in parallel with the degree of histological activity. Therefore, in patients with acute flare, TE examinations should be delayed until ALT levels are stabilized. Regarding this issue, several studies have tried to investigate the optimal period (3 to 6 months) to restore of reliability of TE values in patients with acute flare.

In addition, the performance of TE can be limited in patients with a high body mass index (BMI), or narrow intercostal space, and it is impossible in patients with ascites. In a previous study, BMI >28 kg/m² and waist circumference were significantly associated with TE failure. To achieve technological improvement in these patients, new TE probe (XL Probe) was recently introduced to lessen TE failure rate in obese patients, however its efficacy should be further validated.

CONCLUSION

Over the past decade, significant progress has been made in regarding non-invasive assessment of liver fibrosis in patients with CLD. Of the methods now available, TE appears to be an excellent tool for assessment of liver fibrosis, particularly for diagnosis cirrhosis, and also has prognostic value in longitudinal perspectives. Although TE cannot completely abolish the need for LB, it can be used as an important noninvasive tool which enables us set up a more efficient and tailored management strategies for patients with CLD.

Acknowledgements

This study was supported by the grant of the Good Health R & D Project from the Ministry of Health, Welfare and Family Affairs, Republic of Korea (A102065).

Conflicts of Interest

The authors have no conflicts to disclose.

REFERENCES

1. Bruix J, Sherman M; Practice Guidelines Committee, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. Hepatology 2005;42:1208-1236.
2. European Association For The Study Of The Liver. EASL Clinical Practice Guidelines: Management of chronic hepatitis B virus infection. J Hepatol 2012 Mar 20. [Epub ahead of print].
3. Regev A, Berho M, Jeffers LJ, Milikowski C, Molina EG, Pyrsopoulos NT, et al. Sampling error and intraobserver variation in liver biopsy patients with chronic HCV infection. Am J Gastroenterol 2002;97:2614-2618.
4. Bedossa P, Dargère D, Paradis V. Sampling variability of liver fibrosis in chronic hepatitis C. Hepatology 2003;38:1449-1457.
5. Castera L. Transient elastography and other noninvasive tests to assess hepatic fibrosis in patients with viral hepatitis. J Viral Hepat 2009;16:300-314.
6. Sandrin L, Fourquet B, Hasquenoph JM, Yon S, Fournier C, Mal F, et al. Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. Ultrasound Med Biol 2003;29:1705-1713.
7. Castéra L, Vergniol J, Foucher J, Le Bail B, Chanteloup E, Haaser M, et al. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. Gastroenterology 2005;128:343-350.
8. 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.
9. Bae RC, Cho HJ, Oh JT, Lee EK, Heo J, Shin KY, et al. Clinical factors influencing liver stiffness as measured by transient elastography (Fibroscan) in patients with chronic liver disease. Korean J Hepatol 2010;16:123-130.
10. Lee da M, Moon EJ, Hwang JA, Lee MS, Cheong JY, Cho SW, et al. Factors associated with liver stiffness in chronic liver disease. Korean J Hepatol 2009;15:464-473.
11. Seo YS. Transient elastography, true or false? Korean J Hepatol 2009;15:431-437.
12. Kim SG, Kim YS, Jung SW, Kim HK, Jang JY, Moon JH, et al. The usefulness of transient elastography to diagnose cirrhosis in patients with alcoholic liver disease. Korean J Hepatol 2009;15:42-51.
13. Cho SW, Cheong JY. Clinical application of non-invasive diagnosis for hepatic fibrosis. Korean J Hepatol 2007;13:129-137.
14. 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;29:242-247.
15. 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;54:1758-1763.
16. 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.
17. Kim SU, Han KH, Ahn SH. Non-invasive assessment of liver fibrosis: time to move from cross-sectional studies to longitudinal ones. J Gastroenterol Hepatol 2010;25:1472-1473.
18. Yeh WC, Li PC, Jeng YM, Hsu HC, Kuo PL, Li ML, et al. Elastic modulus measurements of human liver and correlation with pathology. Ultrasound Med Biol 2002;28:467-474.
19. Lucidarme D, Foucher J, Le Bail B, Vergniol J, Castera L, Duburque C, et al. Factors of accuracy of transient elastography (fibroscan) for the diagnosis of liver fibrosis in chronic hepatitis C. Hepatology 2009;49:1083-1089.
20. Kim SU, Seo YS, Cheong JY, Kim MY, Kim JK, Um SH, et al. Factors that affect the diagnostic accuracy of liver fibrosis measurement by Fibroscan in patients with chronic hepatitis B. Aliment Pharmacol Ther 2010;32:498-505.
21. Roulot D, Czernichow S, Le Clésiau H, Costes JL, Vergnaud AC, Beaugrand M. Liver stiffness values in apparently healthy subjects: influence of gender and metabolic syndrome. J Hepatol 2008;48:606-613.
22. 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;105:1116-1122.
23. Kim SU, Choi GH, Han WK, Kim BK, Park JY, Kim do Y, et al. What are ‘true normal’ liver stiffness values using FibroScan?: a prospective study in healthy living liver and kidney donors in South Korea. Liver Int 2010;30:268-274.
24. Arena U, Stasi C, Mannoni A, Benucci M, Maddali-Bongi S, Cambelli D, et al. Liver stiffness correlates with methotrexate cumulative dose in patients with rheumatoid arthritis. Dig Liver Dis 2012;44:149-153.
25. Kim SU, Han KH, Ahn SH. Transient elastography in chronic hepatitis B: an Asian perspective. World J Gastroenterol 2010;16:5173-5180.
26. Arena U, Vizzutti F, Abraides JG, Corti G, Stasi C, Moscarella S, et al. Reliability of transient elastography for the diagnosis of advanced fibrosis in chronic hepatitis C. Gut 2008;57:1288-1293.
27. 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;39:675-684.
28. Siriri R, Sporea I, Bota S, Popescu A, Cornianu M. A comparative study of non-invasive methods for fibrosis assessment in chronic HCV infection. Hepat Mono 2010;10:88-94.
29. 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;26:171-178.
30. Kim SU, Park JY, Kim do Y, Ahn SH, Choi EH, Seok JY, et al. Non-invasive assessment of changes in liver fibrosis via liver stiffness measurement in patients with chronic hepatitis B: impact of antiviral treatment on fibrosis regression. Hepatol Int 2010;4:673-680.
31. Zhu X, Wang LC, Chen EQ, Chen XB, Chen LY, Liu L, et al. Prospective evaluation of FibroScan for the diagnosis of hepatic fibrosis compared with liver biopsy/AST platelet ratio index and FIB-4 in patients with chronic HBV infection. Dig Dis Sci 2011;56:2742-2749.
32. Kim SU, Kim do Y, Park JY, Lee JH, Ahn SH, Kim JK, et al. How can we enhance the performance of liver stiffness measurement using FibroScan in diagnosing liver cirrhosis in patients with chronic hepatitis B? J Clin Gastroenterol 2010;44:66-71.
33. Ogawa E, Furusyo N, Murata M, Ohnishi H, Toyoda K, Tanaih H, et al. Longitudinal assessment of liver stiffness by transient elastography for chronic hepatitis B patients treated with nucleoside analog. Hepatol Res 2011;41:1178-1188.
34. Leroy V, Kim SU. Can transient elastography be used for the management of chronic hepatitis B patients? Liver Int 2012;32:528-530.
35. Yuen MF, Yuan HJ, Hui CK, Wong DK, Wong WM, Chan AQ, et al. A large population study of spontaneous HBeAg seroconversion and acute exacerbation of chronic hepatitis B infection: implications for antiviral therapy. Gut 2003;52:416-419.
36. Vergara S, Macías J, Rivero A, Gutiérrez-Valencia A, González-Serrano M, Merino D, et al. The use of transient elastometry for assessing liver fibrosis in patients with HIV and hepatitis C virus coinfection. Clin Infect Dis 2007;45:969-974.
37. 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;43:1118-1124.
38. Sini M, Sorbello O, Civoli A, Liggi M, Demelia L. Non-invasive assessment of hepatic fibrosis in a series of patients with Wilson’s Disease. Dig Liver Dis 2012;44:487-491.
39. Laharie D, Zeribil F, Adhoute X, Boué-Lahorgue X, Foucher J, Castéra L, et al. Diagnosis of liver fibrosis by transient elastography (FibroScan) and non-invasive methods in Crohn’s disease patients treated with methotrexate. Aliment Pharmacol Ther 2006;23:1621-1628.
40. de Lédénghen V, Douvin C, Kettaneh A, Ziol M, Roulot D, Marcelin 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;41:175-179.
41. Sánchez-Conde M, Montes-Ramírez ML, Miralles P, Alvarez JM, Bellón JM, Ramirez 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;17:280-286.

42. 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;48:963-972.

43. Friedrich-Rust M, Müller C, Winckler A, Kriener S, Herrmann E, Holtmeier J, et al. Assessment of liver fibrosis and steatosis in PBC with FibroScan, MRI, MR-spectroscopy, and serum markers. J Clin Gastroenterol 2010;44:58-65.

44. 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;43:720-728.

45. Barbero-Villares A, Jiménez-Ridruejo JM, Taxonera C, López-Sanromán A, Pajares R, Bermejo F, et al. Evaluation of liver fibrosis by transient elastography (Fibroscan®) in patients with inflammatory bowel disease treated with methotrexate: a multicentric trial. Scand J Gastroenterol 2012;47:575-579.

46. Bray AP, Barnova I, Przemioslo R, Kennedy CT. Liver fibrosis screening for patients with psoriasis taking methotrexate: a cross-sectional study comparing transient elastography and liver biopsy. Br J Dermatol 2012;166:1125-1127.

47. 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;5:1214-1220.

48. 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;134:960-974.

49. Shaheen AA, Wan AF, Myers RP. FibroTest and FibroScan for the prediction of hepatitis C-related fibrosis: a systematic review of diagnosto test accuracy. Am J Gastroenterol 2007;102:2589-2600.

50. Stebbing J, Farouk L, Panos G, Anderson M, Jiao LR, Mandallia S, et al. A meta-analysis of transient elastography for the detection of hepatic fibrosis. J Clin Gastroenterol 2010;44:214-219.

51. Castéra L, Sebastiani G, Le Bail B, de Lédinghen V, Couzigou P, Alberti A. Prospective comparison of two algorithms combining non-invasive methods for staging liver fibrosis in chronic hepatitis C. J Hepatol 2010;52:191-198.

52. Sebastiani G, Vario A, Guido M, Alberti A. Sequential algorithms combining non-invasive markers and biopsy for the assessment of liver fibrosis in chronic hepatitis B. World J Gastroenterol 2007;13:525-531.

53. Sebastiani G, Vario A, Guido M, Noventa F, Plebani M, Pistis R, et al. Stepwise combination algorithms of non-invasive markers to diagnose significant fibrosis in chronic hepatitis C. J Hepatol 2006;44:686-693.

54. 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;43:267-271.

55. Park JI, Park JY, Kim do Y, Park YN, Ahn SH, Chon CY, et al. Prediction of significant fibrosis in chronic hepatitis C patients with normal ALT. Hepatogastroenterology 2011;58:1321-1327.

56. Kim BK, Kim SU, Kim HS, Park JY, Ahn SH, Chon CY, et al. Prospective Validation of FibroTest in Comparison with Liver Stiffness for Predicting Liver Fibrosis in Asian Subjects with Chronic Hepatitis B. PLoS One 2012;7:e35825.

57. Vergniol J, Foucher J, Castéra L, Bernard PH, Tournan R, Terrebonne E, et al. Changes of non-invasive markers and FibroScan values during HCV treatment. J Viral Hepat 2009;16:132-140.

58. Ogawa E, Furusyo N, Toyoda K, Takeoka H, Maeda S, Hayashi J. The longitudinal quantitative assessment by transient elastography of chronic hepatitis C patients treated with pegylated interferon alpha-2b and ribavirin. Antiviral Res 2009;83:127-134.

59. Arima Y, Kawabe N, Hashimoto S, Harata M, Nitta Y, Murao M, et al. Reduction of liver stiffness by interferon treatment in the patients with chronic hepatitis C. Hepatol Res 2010;40:383-392.

60. Wang JH, Changchien CS, Hung CH, Tung WC, Kee KM, Chen CH, et al. Liver stiffness decrease after effective antiviral therapy in patients with chronic hepatitis C: Longitudinal study using FibroScan. J Gastroenterol Hepatol 2010;25:964-969.

61. Fung J, Lai CL, Wong DK, Seto WK, Hung I, Yuen MF. Significant changes in liver stiffness measurements in patients with chronic hepatitis B: 3-year follow-up study. J Viral Hepat 2011;18:e200-e205.

62. Lim SG, Cho SW, Lee YC, Jeon SJ, Lee MH, Cho YJ, et al. Changes in liver stiffness measurement during antiviral therapy in patients with chronic hepatitis B. Hepatogastroenterology 2011;58:539-545.

63. Enomoto M, Mori M, Ogawa T, Fujii H, Kobayashi S, Iwai S, et al. Usefulness of transient elastography for assessment of liver fibrosis in chronic hepatitis B: Regression of liver stiffness during entecavir therapy. Hepatol Res 2010;40:853-861.

64. 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;55:403-408.

65. Vizzutti F, Arena U, Romanelli RG, Rega L, Foschi M, Colagrande S, et al. Liver stiffness measurement predicts severe portal hypertension in patients with HCV-related cirrhosis. Hepatology 2007;45:1290-1297.

66. Castéra L, Le Bail B, Roudot-Thoraval F, Bernard PH, Foucher J, Merrouche W, 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.

67. Kazemi F, Kettaneh A, N’kontchou G, Pinto E, Ganne-Carrie N, Trinchet JC, et al. Liver stiffness measurement selects patients with cirrhosis at risk of bearing large oesophageal varices. J Hepatol 2006;45:230-235.

68. Lemoine M, Katsahian S, Ziol M, Nahon P, Ganne-Carrie N, Kazemi F, et al. Liver stiffness measurement as a predictive tool of clinically significant portal hypertension in patients with compensated hepatitis C virus or alcohol-related cirrhosis. Aliment Pharmacol Ther 2008;28:1102-1110.

69. Kim BK, Han KH, Park JY, Ahn SH, Kim JK, Paik YH, et al. A liver stiffness measurement-based, noninvasive prediction model for high-risk esophageal varices in B-viral liver cirrhosis. Am J Gastroenterol 2010;105:1382-1390.

70. Kim BK, Kim do Y, Han KH, Park JY, Kim JK, Paik YH, et al. Risk assessment of esophageal variceal bleeding in B-viral liver cirrhosis by a liver stiffness measurement-based model. Am J Gastroenterol 2011;106:1654-1662, 1730.

71. Masuzaki R, Tateishi R, Yoshida H, Goto E, Sato T, Ohki T, et al. Prospective risk assessment for hepatocellular carcinoma development in patients with chronic hepatitis C by transient elastography. Hepatology 2009;49:1954-1961.

72. Jung KS, Kim SU, Ahn SH, Park YN, Kim do Y, Park JY, et al. Risk assessment of hepatitis B virus-related hepatocellular carcinoma development using liver stiffness measurement (FibroScan). Hepatology 2011;53:885-894.

73. Fung J, Lai CL, Seto WK, Wong DK, Yuen MF. Prognostic significance of liver stiffness for hepatocellular carcinoma and mortality in HBeAg-negative chronic hepatitis B. J Viral Hepat 2011;18:738-744.

74. Chon YE, Jung ES, Park JY, Kim DY, Ahn SH, Han KH, et al. The accuracy of noninvasive methods in predicting the development of hepatocellular carcinoma and hepatic decompensation in patients with chronic hepatitis B. J Clin Gastroenterol 2012;in press.

75. Kim SU, Lee JH, Kim do Y, Ahn SH, Jung KS, Choi EH, et al. Prediction of liver-related events using fibroscan in chronic hepatitis B patients showing advanced liver fibrosis. PLoS One 2012;7:e36676.

76. Kim SU, Ahn SH, Park JY, Kim do Y, Chon CY, Choi JS, et al. Prediction of postoperative hepatic insufficiency by liver stiffness measurement (FibroScan(R)) before curative resection of hepatocellular carcinoma: a pilot study. J Clin Gastroenterol 2008;42:471-477.

77. Kim SU, Kim YC, Choi JS, Kim KS, Choi GH, Choi JS, et al. Can preoperative diffusion-weighted MRI predict postoperative hepatic insufficiency after curative resection of HBV-related hepatocellular carcinoma? A pilot study. Magn Reson Imaging 2010;28:802-811.

78. Jung KS, Kim SU, Choi GH, Park JY, Park YN, Kim DY, et al. Prediction of recurrence after curative resection of hepatocellular carcinoma using liver stiffness measurement (FibroScan®). Ann Surg Oncol 2012;in press.

79. Rigamonti C, Donato MF, Fraquelli M, Agnelli F, Ronchi G, Casazza G, et al. Transient elastography predicts fibrosis progression in patients with recurrent hepatitis C after liver transplantation. Gut 2008;57:821-827.

80. Carrion 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;12:1791-1798.

81. 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.

82. Corradi F, Piscaglia F, Flori S, D’Errico-Grigioni A, Vasuri F, Tamé MR, et al. Assessment of liver fibrosis in transplant recipients with recurrent HCV infection: usefulness of transient elastography. Dig Liver Dis 2009;41:217-225.

83. Arena U, Vizzutti F, Corti G, Ambu S, Stasi C, Bresci S, et al. Acute viral hepatitis increases liver stiffness values measured by transient elastography. Hepatology 2008;47:380-384.

84. Kim SU, Kim JK, Park YN, Han KH. Discordance between liver biopsy and Fibroscan® in assessing liver fibrosis in chronic hepatitis B: risk factors and influence of necroinflammation. PLoS One 2012;7:e32233.

85. 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;14:360-369.

86. Fung J, Lai CL, But D, Hsu A, Seto WK, Cheng C, et al. Reduction of liver stiffness following resolution of acute flares of chronic hepatitis B. Hepatology 2010;41:217-225.

87. Park H, Kim SU, Kim do Y, Ahn SH, Han KH, Chon CY, et al. Optimal time for restoring the reliability of liver stiffness measurement in patients with chronic hepatitis B experiencing acute exacerbation. J Clin Gastroenterol 2012;in press.

88. Foucher J, Castéra L, Bernard PH, Adhoute X, Laharie D, Bertet J, et al. Prevalence and factors associated with failure of liver stiffness measurement using FibroScan® in a prospective study of 2114 examinations. Eur J Gastroenterol Hepatol 2006;18:411-412.

89. de Ledinghen V, Wong VW, Vergniol J, Wong GL, Foucher J, Chu SH, et al. Diagnosis of liver fibrosis and cirrhosis using liver stiffness measurement: comparison between M and XL probe of FibroScan®. J Hepatol 2012;56:833-839.