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THE CLINICAL FEATURES OF TRANSIENT ELASTOGRAPHY (FIBROSCAN) EXAMINATION AMONG LIVER DISEASES PATIENTS AT GASTROENTEROHEPATOLOGY DIVISION OF DR. SOETOMO HOSPITAL, SURABAYA

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ABSTRACT

Until now liver biopsy is still gold standard to asses liver fibrosis. Fibroscan within superiority and little limitation can be an alternative as non-invasive procedure to asses liver fibrosis. In this pioneer study among "various chronic liver disease patients at Dr Soetomo hospital resulted higher Fibroscan score of liver stiffness, whereas the highest score of liver stiffness revealed among respectively hepatoma, liver cirrhosis, chronic hepatitis C, chronic hepatitis B, and NAFLD. For future, It is important to enrollment similar study that involved bigger sample size to determine liver fibrosis among any various liver diseases and conjuncted to detect its clinical complication earlier.

Keywords: *transient elastography, Fibroscan, liver disease, fibrosis*

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INTRODUCTION

The accurate evaluation of hepatic histopathology and function is vital for treatment decisions and prognostication in patients with all forms of liver disease. Liver fibrosis is a common pathway for a multitude of liver pathologist and associated with morbidity and mortality. The final stage, cirrhosis lead to numerous complication (oesophageal varices and hemorrhages, ascites, cancer, death). The diagnosis of liver fibrosis is relevant for estimation of prognosis, surveillance and treatment decision in patients with chronic liver disease. Untill recently, assessments of liver injury, fibrosis and steatosis have generally required liver biopsy, whereas evaluations of have relied on routine biochemichal assays (Nusi, 2005; Myers, 2008).

Liver biopsy has been considered the traditional gold standard for the evaluation of chronic liver disease and a percutaneous liver biopsy often has been done safely either with or without radiologic guidance. However, biopsy is an invasive and potentially painful procedure and carries a small risk of morbidity and death. It is recognized that liver biopsy samples performed with the larger bore needles are needed to accurately stage and grade the extent of liver injury. Furthermore, with better clinical argument, the advent of specific serologic testing and improved radiologic modalities, the need for liver biopsy has been questioned in some clinical scenarios such as hepatitis B, hepatitis C, non alcoholic fatty liver disease and hepatocellular carcinoma (Reddy, 2008).

Among the most important aspects of histopathological assessment in the setting of chronic liver disease are the determination of the degree of fibrosis (stage) and necroinflammation (grade). Since fibrosis and necroinflammation constitute anatomical damage to liver parenchyma, liver biopsy is by definition the only approach enabling their direct assessment. All invasive methods are surrogate techniques and whatever their accuracy, suffer from a lack of specificity (Bedossa, 2008).

Assessment of liver injury, fibrosis, and steatosis generally required liver biopsy (METAVIR score) as gold standard. Although liver biopsy has long been regarded as the gold standard, there are obvious limitations to this procedure that characterized : invasive and painful, costly, and having risk of complications (major hemorrhage and death), sampling error (sample ability only 1 : 50,000 of the liver), variability in pathological interpretation, and difficulty to perform repeated procedure to track hepatic injury. It represent an approximation of liver fibrosis of the whole liver and is therefore, not gold standard fibrosis assessment, but the best currently available procedure.

However, and because non-invasive tests are not independent of liver biopsy in that they have been tuned to match assessment of fibrosis through liver biopsy, these limitation also affect the performance of non-invasive test (Bedossa, 2008)

The majority of the literature examining non-invasive measures of hepatic pathologiy has been focused on liver fibrosis. These tools can be broadly classified as serological assays, elastrography and other imaging methods, and high –throughoutput technologies including genomics, proteomics, and glycomics (Myers, 2008).

Table 1. Characteristics of the ideal fibrosis marker (Myers, 2008) :

- Liver specific
- Applicable to all types of liver disease
- Independent of metabolic alterations (e.g. impaired biliary or renal excretion and reticuloendothelial function)
- Valid measurement of the stage of fibrosis, the degree of matrix deposition, and / matrix removal
- Sensitive enough to distinguish individual stages of fibrosis
- Easy to perform and acceptable to patients and physicians
- Inexpensive
- Reproducible
- Responsive to change in fibrosis attributable to therapy or natural history of the disease
- Correlated with clinical outcomes (e.g. liver-related morbidity and mortality)

Transient elastography (TE)

TE (Fibroscan ®), is relatively novel approach to measure liver stiffness – a surrogate for liver fibrosis – has gained increasing clinical use (Sandrin, 2003). Over the past few years transient elastography (TE) has emerged as highly useful noninvasive form that has been touted to be helpful in assessing the stage of fibrosis. Elastography has been developed on the principle that livers with increasing degrees of scarring have decreasing elasticity and that a shear wave propagating through stiffer material would progress faster than in one with more elastic material (Sandrin, 2003). The transient nature of measuring the shear wave (~ 100 miliseconds) is ideal as the liver's position moves with breathing, and other reflected elastic waves can be excluded from analysis by this method (Reddy, 2008)

The elastography device is a vibrating probe with an ultrasound transducer on its end. This transducer emits a shear wave of low frequency of 50 Hz and "pulse-echo ultrasound acquisitions" are used to measure the amount of time the wave takes to go through a set "window" of tissue. The amount of tissue scanned is 1cm to 5 cm, an area that is 100 times the size of a standard biopsy. Stiffness is measured by the shear modulus, which uses units of kilopascals or kPa (Malik, 2007).

The velocity of this wave (measured using pulse-echo US acquisition) is proportional to liver stiffness. The stiffness is measured by the shear modulus, which uses units of kilopascals (kPa). Stiffer and fibrotic livers are associated with faster wave propagation. The result of the scan is expressed as the median of 10 successful acquisitions; liver stiffness values range from 2.5 to 7.5 kPa. Since TE measures liver stiffness in a volume approximating a 1 cm wide by 4 cm long cylinder - roughly 100 times greater than typical liver biopsy – it is likely more representative of the entire hepatic parenchyma (Castera, 2008). TE is entirely noninvasive, takes only 5 minutes to complete, can be reliably performed following a short training period (~ 50 examinations are necessary for competency), and can be readily integrated into an outpatient hepatology clinic. Both the intra – and inter- observer coefficient of variations are low (~3%) indicating very good reproducibility (Sandrin, 2003).

Since originally described in 2003, numerous publications have assessed the performance characteristics of TE across a broad spectrum of liver disease. These studies have demonstrated a strong correlation between liver stiffness values and the stage of hepatic fibrosis (Sandrin, 2003 ; Castera, 2008). In a recent systemic review of 50 studies, reported summary AUROCs (95% CI) for the diagnosis of significant fibrosis (> F2), severe fibrosis (> F3), and cirrhosis respectively of 0.84 (0.82-0.86), 0.89 (0.91 – 0.99), and 0.94 (0.93 – 0.95). Despite these high AUROCs, however it is important to note that a considerable overlap in TE values has been observed for adjacent satges of hepatic fibrosis. This has important implications for the definition of threshold values for specific fibrosis stages, and has contributed to heterogenous results across studies and conditions. For examples, in this meta-analysis, diagnostic threshold values to define a positive test varied between 4.5 to 11.8 for F2 – F4 fibrosis and 10.1 to 19.00 for cirrhosis (Friedrict-Rust, 2008).

A recent metaanalysis of nine studies concluded that it reliably diagnosed cirrhosis and had a sensitivity of 87% and specificity of 91%. So, the ability to diagnose lesser degree of fibrosis was not as good (Talwalkar, 2007). TE has important implications for the staging of fibrosis in an individual patient and supports the use of ranges values rather than a single threshold value in clinical

practice. For example. When liver stiffness values are less than 7 kPa meaning no or minimal fibrosis, whereas cirhhosis is likely when the values exceed 12.5 kPa (Castera, 2007).

Apart from it being a non-invasive tool with low operating costs, this technology has been suggested by those experienced in its use, to have good reproducibility. The technique however maybe limited in whom an adequate intercostals window cannot be obtained which then would apply to the obese patients and particularly those a BMI 40 over (Reddy, 2008). Several caveats warrant mention when discussing the utility of TE. First, technical failure occurs in approximately 5% of patients, including in those with ascites, narrow intercostal space, and obesity/thick chest wall (Castera, 2005 ; Kettaneh, 2007). Second, studies have suggested that TE results may be influenced by ALT flares. A study among 18 patients with acute viral hepatitis and no prior history of liver disease reported, as the hepatitis resolved, a progressive normalization of liver stiffness in parallel with the fall in transaminases was observed (Arena, 2008). The aim is this study is to determine the clinical features of transient elastography (fibroscan examination) among patients with various chronic liver diseases at Gastroenterohepatology of Dr Soetomo Hospital

MATERIALS AND METHODS

The inclusion criteria were patients with chronic liver disease (chronic hepatitis B, chronic hepatitis C), non-alcoholic fatty liver disease (NAFLD), cirrhosis, and hepatoma/hepato cellular carcinoma (HCC). The exclusion criteria were ascites, obesity, and patients with narrow intercostals space. This was a cross-sectional study using descriptive design, performed between April – October 2009. The undertaken laboratory tests were AST (IU/ml), ALT (IU/ml), platelet, HBSAg, anti-HCV, abdominal ultrasonography (to assess liver cirrhotic), and FibroScan ~ (Echosen-Paris)

Fibroscan Techniques

The patient was positioned in dorsal decubitus position. The right arm was in maximal abduction, and the measurement was performed on the right lobe of liver between the rib bone. The operator was sitting on a chair with wheels on the right side of the patients, facing both the patient's chest and device's screen. The probe was placed the probe between the rib bone, opposite right lobe liver in the middle of parenchyme and far from liver border. Location of probe to liver is about to that of the Liver biopsy, that is a location with dullness at percussion and between sternum and mid axillary line (MCL). Keep Probe perpendicular to the skin surface, by probe M (medium) in frequency of 3.5 MHz, and examination depth of 25 mm – 65 mm (4 cm)

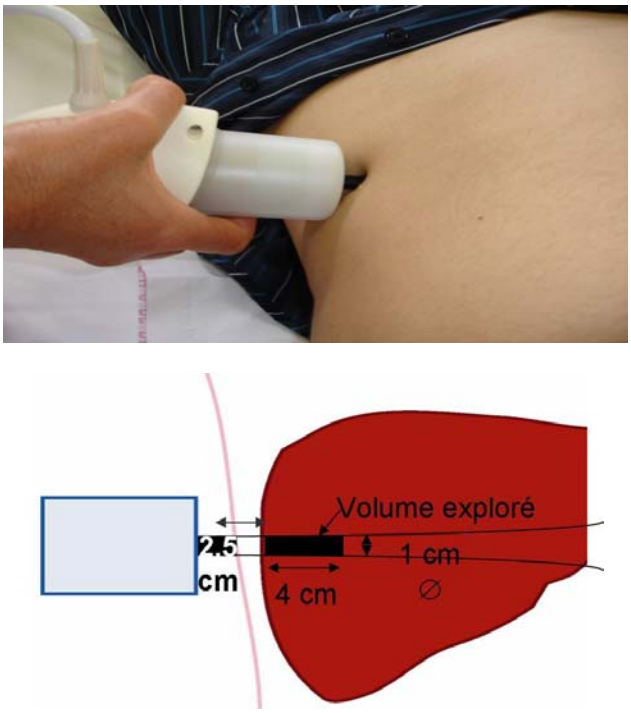

Figure 1. Fibroscan Techniques

RESULTS

A total of 60 patients with various liver diseases has been envolved with transient elastography (fibroscan examinations) consist of 23 women (38%) and 37 men (62%) within mean of the age was 46.9 + 14.3 years old.

Table 1. Sample characteristics

	Mean ± SD	Median (minimum – maximum)
Sex	Men = 37 (62%)	Women = 23 (38%)
Age (years old)	46.9 ± 14.3	46 (16 – 74)
AST (IU)	93.41 ± 102.91	65.50 (14 – 680)
ALT (IU)	90.87 ± 126.9	51.50 (8 – 743)
Platelet (mm^3/dL)	206.42 ± 121.30	190 (13 – 527)

The diagnosis liver diseases patients (60 patients) before them performed transient elastography (fibroscan) examination consist of : chronic hepatitis viral B (26%),

non alcoholic fatty liver disease or NAFLD (23%), chronic hepatitis C (17%), hepatocellular carcinoma or hepatoma (12%), liver cirrhosis (10%) and non specific/others (12%).

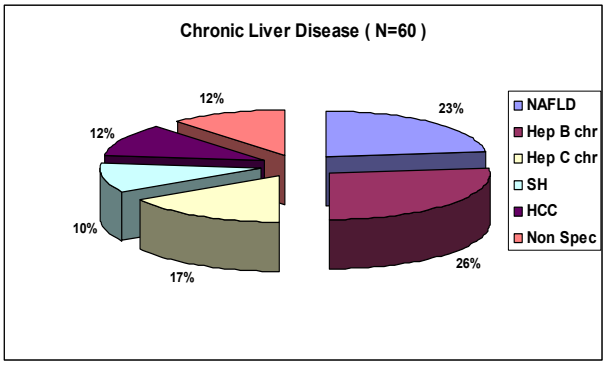

Figure 2. The distributions of sample disease

DISCUSSION

In healthy subjects, one study among 429 patients without risk factors for liver disease, the values of liver stiffness vary from 1.5 to 10.9 kPa, where the average = 5.5 + 1.6 kPa. (Roulot, 2008). The normal liver stiffness value for healthy individuals being around 5.5 kPa. The age of the subject doesn't affect liver stiffness and males tend to have a slightly higher liver stiffness value compared to females (Roulot, 2008).

Table 2. The features of Fibroscan examination

Population	N	Fibroscan (kPa) Mean ± SD	Fibroscan (kPa) Median (min –max)
Fatty liver	14	8.05 ± 3.67	6.8 (4.5 - 15.6)
Hepatitis B chronic	16	18.61 ± 16.45	12.9 (4.8 – 62.90)
Hepatitis C chronis	10	18.85 ± 7.84	18.10 (6.8 – 36.3)
Liver Cirrhosis	6	36.56 ± 21.69	29.70 (17.30 – 70.60)
Hepatocellular Carcinoma	7	58.41 ± 20.07	70.60 (30.50 – 75)
Non-specific / others	7	16.14 ± 26.16	5.3 (3.4 – 75)

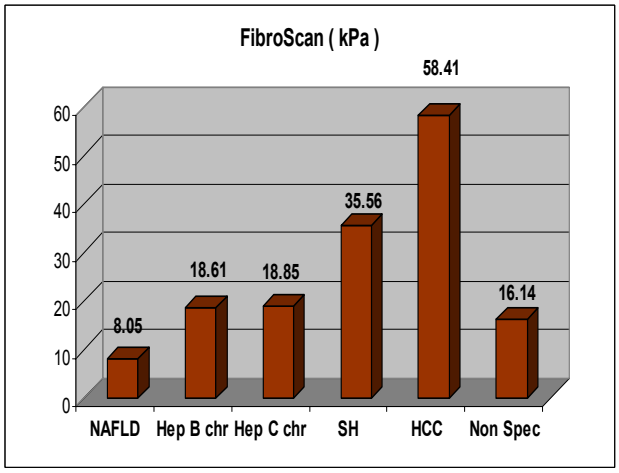

Figure 3. The result of fibroscan examinations

NAFLD

Arena et al reported in a study that hepatic steatosis does not have significant impact on liver stiffness although obesity can predispose to transient elastography (TE) failure (Myers, 2008). A study that enrolled by 97 NAFLD patients with fibroscan and liver biopsy, by multivariate analysis resulted that steatosis and acitivity didn't influence liver stiffness, and found cutt of point significant fibrosis (F>2), advanced fibrosis (F >3), and cirrhosis (F=4) respectively 6.7 kPa, 9.8 kPa and 17.5 kPa within AUROC respectively 0.87, 0.90 and 0.99. First result in NAFLD are promising for the assessment of liver fibrosis and need to be confirmed in a larger cohort including obese patients (Yoneda et al, 2008). In our study, 14 patients NAFLD who underwent TE without any information their fibrosis staging, BMI, or transaminase level, the value of liver stiffness is 8.05 + 3.67 kPa

Chronic hepatitis B

One of the important aspects of liver stiffness measurements is the cutt-off values that are adopted for different stages of fibrosis, with higher cutt-off levels corresponding to higher fibrosis stages. The cutt –off levels are also different for different cases. A study among patients with chronic hepatitis B found cutt of point significant fibrosis (F>2), advanced fibrosis (F >3), and cirrhosis (F=4) respectively 7.2 kPa, 8.1 kPa and 11.0 kPa within AUROC respectively 0.81, 0.93 and 0.93 (Marcellin, 2009). In our study, 16 patients with chronic hepatitis B without cirrhotic who

underwent TE showed the value of liver stiffness is 18.61 + 16.45 kPa.

Chronic hepatitis C

A study among patients with chronic hepatitis C revealed cut-off point significant fibrosis (F>2), advanced fibrosis (F >3), and cirrhosis (F=4) respectively 8.8 kPa, 9.6 kPa and 14.6 kPa within AUROC respectively 0.79, 0.91 and 0.97 (Ziol, 2005). Other study within subjects chronic hepatitis C patients revealed cut-off point significant fibrosis (F>2), advanced fibrosis (F > 3), and cirrhosis (F=4) respectively 7.1 kPa, 9.5 kPa and 12.5 kPa within AUROC respectively 0.83, 0.90 and 0.95 (Castera, 2005). In our study, 10 patients with chronic hepatitis C without cirrhotic who underwent TE showed the value of liver stiffness is 18.85 + 7.84 kPa.

Cirrhosis

TE has important implications for the staging of fibrosis in an individual patient and supports the use of ranges values rather than a single threshold value in clinical practice. When liver stiffness values are less than 7 kPa meaning no or minimal fibrosis, whereas cirhhosis is likely when the values exceed 12.5 kPa (Castera, 2007). Metaanalysis based on 9 studies resulted the pooled estimates for the diagnosis of cirrhosis by TE (fibroscan) were excellent: sensitivity 87% (95% CI , 84% - 90%), specificity 91% (95% CI, 89% - 92%). Reported that TE cutt off for cirrhosis range from 10.3 kPa in chronic hepatitis B, and 17.3 kPa in chronic cholestatic diseases. It has been suggested that TE cutt-off values could be optimized if specifically defined for each aetiology (Talwaker, 2007). Other meta analysis resulted from 35 studies with various etiology, the AUROC (95% CI) with cutt-off point of diagnosis significant fibrosis (F>2), advanced fibrosis (F>3) and cirrhosis (F=4) respectively were 0.84 (0.82-0.86) with 7.65 kPa, 0.89 (0.88-0.91) with NR, and 0.94 (0.93-0.95) with 13.01 kPa (Fredrich-Rust, 2008).

In a recent systemic review of 50 studies, reported summary AUROCs (95% CI) for the diagnosis of significant fibrosis (> F2), severe fibrosis (> F3), and cirrhosis respectively of 0.84 (0.82-0.86), 0.89 (0.91 – 0.99), and 0.94 (0.93 – 0.95). Despite these high AUROCs, however it is important to note that a considerable overlap in TE values has been observed for adjacent satges of hepatic fibrosis. In this meta-analysis, diagnostic threshold values to define a positive test varied between 4.5 to 11.8 for F2 – F4 fibrosis and 10.1 to 19.00 for cirrhosis (Friedrict-Rust, 2008).

For 4 month period, among 200 patients with chronic liver disease with varying aetiology (HCV, HBV, alcohol-related, NASH, others) underwent TE and liver biopsy revealed the mean (SD) liver stiffness value was 10.6 (11.5) kPa (range 2.4 to 75 kPa). Using ROC curves, three threshold value for TE were identified : > 7.9 kPa for marked fibrosis (F>2; sensitivity 72%, specificity 84%); > 10.3 kPa for severe fibrosis (F>3; sensitivity 76%, specificity 90%), and > 11.9 kPa for Cirrhosis (sensitivity 91% and specificity 89%). (Fraquelli M, 2007). In a study of 711 patients with chronic liver disease (n= 95 with cirrhosis), demonstrated a significant correlation between liver stiffness values and biochemical test (platelet, albumin, bilirubin), the child-Pugh score, and clinical parameter (history of ascites, hepatocellular carcinoma) (Foucher, 2006). In our study, 6 patients with liver cirrhotic (based on ultrasound examination) who underwent TE showed the value of liver stiffness is 36.56 + 21.69 kPa.

REFERENCES

Arena U, Vizzutti F, Corti G, Ambu S, Stasi C, Bresci S, Moscarella S, Boddi V, Petrarca A, Laffi G, Marra F, Pinzani M. Acute Viral Hepatitis Increases Liver Stiffness Values Measured by Transient Elastography. Hepatology 2008 ; 46: 628-634

Castera L, Forns X, Alberti A. Non-Invasive Evaluation of Liver Fibrosis Using Transient Elastography. J Hepatol 2008; 48 : 835-847

Castera L, Veginol J, Foucher J, Le Bail B, Chanteloup E, Haaser M, Darriet M, Couzigou P, De Ledinghen V. Prospective Comparison of Transient Elastography, Fibrotest, APRI, and Liver Biopsy for the Assessment of Fibrosis in Chronic Hepatitis C. Gastroenterology 2005; 128 : 343-350

Castera L, Verginol 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(2) : 343-350

Foucher J, Chanteloup E, Verginiol J, castera L, Le Bail B, Adhoute X, bertet J, Couzigou P, de Ledinghen V. Diagnosis of Cirrhosis by Transient Elastography (Fibroscan) : A Prospective Study. Gut 2006; 55 : 403-408

Friedich-Rust M, Ong MF, Martens S, Sarrazin C, Bojunga J, Zeuzem S, Herrmann E. Performance of Transient Elastography for the Staging of Liver Fibrosis : a meta-analysis. Gastroenterology 2008; 134 : 960-974

K. Rajender Reddy. Controversy : Is Liver Biopsy still Necessary for Injury and Fibrosis Assessment? (Con). The Changing Face of Hepatology, post graduate

course, AASLD, San Fransisco, California Oct 31st – Nov 1st, 2008

Kettaneh A, marcellin P, Douvin C, Poupon R, Ziol M, Beaugrand M, de Ledinghen V. Features associatiated with Success rate and Performance of Fibroscan Measurement for the Diagnosis of Cirrhosis in HCV Patients. J Hepatology 2007; 46 : 628-634

M. Yoneda et al. Transient Elastography in Patients with Non-Alcoholic Fatty Liver Disease (NAFLD). Gut 2007; 46 (4): 543-545

Malik R, Afdhal NH. Stiffness and Impedance : the New Liver Biomarkers. Clin Gastroentero Hepatology 2007 ; 5: 144-146

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 (2) : 48-54

Mirella Fraquelli, C. Rigamonti, G Casazza, Dario Conte, Maria F Donato, G Ronchi, M Colombo. Reproducibility of Transient Elastography in the Eavluation of Liver Fibrosis in Patient. Gut 2007; 57 : 968-973

Nusi IA. : Non Alcoholic Steato Hepatitis (NASH) patients without Diabetes Mellitus and Obesity with good response to treatment.Folia Medica Indonesiana, Vol 41 No.2., April – June 2005.

Pierre Bedossa. Controversy : Is Liver Biopsy still Necessary for Injury and Fibrosis Assessment? (Pro). The Changing Face of Hepatology, post graduate course, AASLD, San Fransisco, California Oct 31st – Nov 1st, 2008

Robert P. Myers. Diagnostic Tools in the Assessment of Liver Injury, Fibrosis, Steatosis, and Function : The Changing Face of Hepatology, post graduate course, AASLD, San Fransisco, California Oct 31st – Nov 1st, 2008

Roulot D, Czernichow S, Le Clesiau H, Costes JL, Vergnaud AC, Beaugrand M. Liver Stiffness values in Apparently Healthy Subjects : Influence of Geneder and Metabolic Syndrome. J Hepatol 2008; 48 (4) : 606-613

Roulot D, S. Czernichow, et al. Is Liver Stiffness Measurement an Appropriate Screening Method to Detect Liver Fibrosis in the General Populations? 43rd Annual Meeting of the European Association for the Study of the Liver, April 23rd – 27th 2008

Sandrin L, Fourquet B, Hasquenoph JM, Yon S, Fournier C, Mal F, Christidis C, Ziol M, Poulet B, Kazemi F, Beaugrand M, Palau R. Transient Elastography : a New Non-Invasive Method for Assessment of Hepatic Fibrosis. Ultrasound Med Biol 2003 : 29 : 1705-1713

Talwalkar, J.A. Elastography for Detecting Hepatic Fibrosis : option and considerations. Gastroenterology 2008 ; 135 (1) : 299-302

Ziol M, Handra-Luca A, Kettaneh A, et al. Non-invasive Assessment of Liver Fibrosis by Measurement of Stiffness in Patients with Chronic Hepatitis C. Hepatology 2005 ; 41 (1) : 48-54.