AUSTRALIAN LIVER ASSOCIATION (ALA) EXPERT CONSENSUS RECOMMENDATIONS FOR THE USE OF TRANSIENT ELASTOGRAPHY IN CHRONIC VIRAL HEPATITIS

W. Kemp[1], M Levy[2], M. Weltman[3], J. Lubel[4,5]

On behalf of the Australian Liver Association (ALA)

[1]Alfred Hospital, Department of Gastroenterology, Melbourne, Vic, Australia; [2]Liverpool Hospital Gastroenterology Department, NSW, Australia; [3]Nepean Hospital Gastroenterology Department, NSW, Australia; [4]Eastern Health Department of Gastroenterology & Hepatology, Melbourne, Vic Australia; [5]Eastern Health Clinical School, Monash University, Melbourne, Vic, Australia

Correspondence

Dr William Kemp MBBS FRACP PhD
Department of Gastroenterology
Alfred Hospital
Commercial Rd
Prahran, Vic, Australia 3181
w.kemp@alfred.org.au
Ph: 03 90763375
Fax: 03 90762194

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/jgh.12865

Acknowledgments

This document was commissioned by the Australian Liver Association (ALA). No Financial support was sought or received for the preparation of this document. The authors have no financial disclosures in relation to the contents of this document. This document is however the result of a collaborative and inclusive process and therefore the authors would like to acknowledge the input of Associate Professor Amany Zekry and the ALA executive committee in addition to Associate Professor Joe Torresi and the Victoria Hepatitis Special Interest Group (VHSIG). The authors also acknowledge Dr Laurent Castera for his considered comments. The authors accept responsibility for the accuracy of the manuscript and any opinions stated are those of the authors.

The technique of Transient Elastography (TE) using FibroScan® (Echosens, Paris) represents one of a range of non-invasive tools specifically developed for the estimation of the degree of hepatic fibrosis. However, several unique features of this device have resulted in a rapid uptake of this technology since its introduction into Australia in 2008. These features include; simplicity of operation, speed of assessment and a high degree of safety and tolerability. The result is a test with attributes suitable for use in clinical practice. Currently it is estimated that there are in excess of 80 FibroScan® machines in operation across all states and territories of Australia. Despite the rapid uptake of TE and other non-invasive tools to estimate hepatic fibrosis, it is perhaps somewhat surprising that there are no specific guidelines governing the use of these tools, nor the interpretation of the results. The integration into clinical practice has therefore evolved without regulation and without a consensus on the appropriate role these technologies have in clinical management. In recognition of this deficiency, the Australian Liver Association (ALA) requested the development of "expert statements" for the use of TE in clinical practice. A review of the literature and proposal of recommendations to be included in the consensus statement was presented at Australian Gastroenterology Week (AGW) 2013, Melbourne, Australia. Input from key stakeholders and interested parties were encouraged. The recommendations regarding the use of TE included in this document are derived from this process and are intended to assist the clinician by summarizing the relevant published data and presenting some practical guidance for the use of TE.

It is recognised that measurement of liver stiffness by elastography is a continually evolving area and new research and new technological advances are

likely to impact upon clinical practice. For example the advent of Real Time Elastography (Hi RT-E, Hitachi), Magnetic Resonance Elastography (MRE), Acoustic Radiation Force Impulse (ARFI; Virtual Touch, Siemens) and Shear Wave Elastography (SWE; Aixplorer, Supersonic) represent important and innovative developments although their place in the armamentarium of non-invasive tools remains to be determined. Due to their limited accessibility the current document and recommendations are specific for the use of TE.

Practicalities of TE

Obtaining a valid assessment

The measurement of liver stiffness using FibroScan has been well described.[1, 2] In brief, this device measures the velocity of a shear-wave generated by a transducer that is incorporated into an ultrasonic probe. The shear-wave velocity can be converted into a measure of liver stiffness according to the equation $3\rho V^2$, where V is the shear velocity and ρ is the mass density (constant for tissues).[3] The unit of measurement is kilopascals (kPa) and the calibration of the device allows readings to range from 1.5 kPa – 75 kPa. The results are expressed as the median of the individual liver stiffness measurements (LSM) and interquartile range (IQR). Somewhat arbitrarily, a reliable TE assessment has been defined as an assessment fulfilling three characteristics:

1. A minimum of 10 readings
2. A success rate of measurements ("shots") ≥ 60%
3. An IQR/median ratio (IQR/M) of ≤ 0.30

By convention, TE failure is deemed to occur when no readings are obtained after 10 shots. TE failure occurs in 2.1-3.1% of examinations. [4, 5] Furthermore, according to the large Castera series,[4] unreliable readings occur in about 16% of

examinations. Independent variables associated with unreliable readings are: BMI > 30 kg/m^2, operator experience fewer than 500 examinations, age > 52 years, female gender, systemic hypertension and the presence of type 2 diabetes. Overall a reliable assessment is not achieved in approximately 1 in 5 TE examination, representing a significant limitation of this technology compared to biomarkers and possibly other elastography techniques.

In order to minimize the number of patients with unreliable readings, several probe types have been developed; S probe (5MHz transducer, measurement of liver stiffness take place between 15 to 50 mm), M probe (3.5 MHz transducer, measurement of liver stiffness take place between 25 to 65 mm) and XL probe (2.5 MHz transducer, measurement of liver stiffness take place between 35 to 75 mm). Reliable TE assessment can be achieved in over 90% of adults when both the M and XL probe are used as required.[6] Because the M probe takes measurements between 25 to 65 mm from the probe, those patients with a skin-to-capsule distance (SCD) of > 25mm should be assessed with the XL probe. In practice < 8% of patients with a BMI < 30 kg/m^2 have a SCD > 25mm. The rate of SCD > 25mm increases to 50% for patients with a BMI between 35-40 kg/m.[27] It is also relevant to note that several studies have demonstrated that LSMs taken with the XL probe are lower than that obtained by the M probe[6, 8] by a median of 1.4 kPa.[7]

Several studies have demonstrated the importance of the IQR/M as a marker of the accuracy of TE in correctly classifying patients. [9-11] The recent study by Boursier et al,[11] found that TE reliability was a function of two variables; the LSM and the IQR/M. In this large study including over 1000 patients with a variety of liver diseases, the presence of an IQR/M > 0.30 and LSM median ≥ 7.1 kPa

provided accuracy (as determined by AUROC) lower than that of the whole study population and were therefore considered "poorly reliable." Conversely, the highest accuracy was observed in the group with an IQR/M ≤ 0.10 regardless of the LSM. These data serve to highlight the importance of using IQR/M as a marker of test reliability.

TE training

Whilst the technique of TE is simple to learn,[12] and has a high degree of inter and intra-observer agreement,[13] there is evidence to support the concept that operator experience is a factor in obtaining a valid assessment. In a large review based on over 13,000 TE examinations, Castera and colleagues[4] found that operator inexperience (defined as < 500 examinations) was independently associated with both LSM failure (OR 2.5 [CI95%;1.6-4.0]) and reading unreliability (OR 3.1 [CI95%;2.4-3.9]). In one of the largest studies comparing TE and liver biopsy in a population of patients with either hepatitis B or C,[14] there was no difference in the performance of TE (as determined by AUROC) between physician performed TE and a trained technician. This demonstrates that an appropriately trained individual with suitable experience can perform the technique in a reliable manner. There is no structured training program or credentialing currently available in Australia, nor has the optimal number of examinations required for competence and independent practice been determined. Familiarity with the device can be achieved with as few as 50-100[5, 12] examinations although operator experience is an established factor in TE accuracy.

TE and fasting

The early descriptions of FibroScan® described the performance of this test in the non-fasting state.[1] However in recent years several studies have demonstrated the impact that food intake has on liver stiffness.[15-17] The mechanism underpinning this phenomenon remain to be fully elucidated however it has been postulated that the changes may be at least in part influenced by post-prandial variations in the portal venous and hepatic arterial blood flow.[16] The magnitude of the increase in LSM post meal ingestion may be related to the stage of hepatic fibrosis (Maximum ΔLSM for F0-1 vs F2-3 vs F4 was 1.9 kPa, 2.7 kPa and 4.7 kPa respectively). Liver stiffness returned to baseline levels within 120 minutes in all patients independently of the stage of fibrosis.[15]

Result interpretation

TE provides a measure of liver stiffness on a continuous scale from 1.5 kPa – 75 kPa. The validation of this test was performed using liver biopsy as the reference standard. A potential criticism is that LSM expressed on a continuous scale attempts to predict histological stage which is generally expressed as an ordinal scale (Metavir F0 to F4).[18] The optimal cut-offs have been determined from the ROC (receiver operating characteristic) curve and therefore represent a compromise between sensitivity and specificity. Meta-analysis of multiple studies suggest best cut-offs to identify cirrhosis or rule out significant fibrosis.[19] However, when considering data obtained from the ROC curves, it is also important to be cognisant of the inherent inconsistencies in liver biopsy assessment. [20-22] Since errors in the LSM obtained by TE and errors in liver biopsy assessment are independent of each other, the observed sensitivity and specificity of TE in assessing the "true" liver fibrosis stage is likely to be

underestimated.[23] Moreover, it is not surprising that there is substantial overlap between the interquartile ranges around the LSM median values relating to each METAVIR stage because the histological evolution from normal liver to cirrhosis is described with a categorical scoring systems that reflect the location (not quantity) of fibrosis and architectural disturbance.[24] This degree of complexity has resulted in variations in TE interpretation. As yet there is no broadly accepted method for TE result interpretation although most centers report according to published "cut-offs" for specific disease aetiologies. The ability of LSM to estimate the risk of hard clinical end points such as death and decompensation,[25] portal hypertensive complications[26, 27] and hepatocellular carcinoma,[28, 29] may be a more powerful use of TE than distinguishing between the early stages of liver fibrosis. In addition, when reporting according to "cut-offs" the clinician should appreciate that any particular LSM is associated with a spectrum of probabilities for each fibrosis stage (Figure 1).[15, 30] We suggest that the TE result should be interpreted in the clinical context utilising a "pre-test" probability for the stage of hepatic fibrosis.[31] For example, when the pre-test probability of cirrhosis is low (< 25%) even a positive test cannot confirm cirrhosis as perhaps 25-30% of such individuals will not have cirrhosis. In this setting where there is a discrepancy between the clinical impression and the LSM, a second non-invasive test or a liver biopsy may be of clinical benefit. If however the pre-test probability for cirrhosis is high (>75%) then a positive tests allows a diagnosis of cirrhosis to be made with a high degree of certainty (post-test probability > 95%).

Interpretation of TE must also take into account variables that are known to influence LSM beyond that of liver fibrosis. These factors include: hepatic

inflammation,[32] cholestasis,[33] hepatic congestion and other factors that may increase tension within Glisson's capsule such as the presence of space occupying lesions. The effect of hepatic steatosis is still debated.

Consensus Recommendations

1. *TE should be performed according to a standardized protocol consistent with existing guidelines with the patient in the supine position, right arm in full abduction.*
2. *The reference site of LSM is the midaxillary line in the first intercostal space below the liver dullness upper limit. The phase of respiration may be relevant and should be taken into account.*
3. *The patient should fast for at least 2 hours prior to the procedure*
4. *The M probe is suitable for most patients but ideally the XL probe should be used for patients with a skin-to-capsule distance of > 25mm.*
5. *A reliable assessment must include an IQR/M of ≤ 0.30. We also strongly recommend a minimum of 10 valid shots. The evidence supporting a 60% success rate is weak however, for consistency with international standards and for research purposes, this is desirable.*
6. *There is reasonable evidence indicating TE can be performed in a reliable way by both physicians and technicians, however a learning curve is apparent. At this stage no specific recommendations can be made regarding the number of training examinations that should be performed before independent practice. Operator experience is however a factor determining TE accuracy and expert proficiency may require > 500 examinations.*
7. *Result interpretation should be mindful of the error inherent to both liver biopsy and non-invasive technologies such as TE. It should be appreciated*

that LSM is a guide to severity of fibrosis and ideally results should be expressed in terms of probability rather than certainty. We recommended against using terms such as "normal" or "no-fibrosis" due to the overlap between early fibrosis stages, "no or minimal fibrosis" would be more accurate. Consistent with most investigations and diagnostic tests, LSMs need to be considered in light of the clinical context and interpreted accordingly.

8. *TE / other non-invasive tools and liver biopsy should be used in an integrated way to allow safe, accurate and timely evaluation of patients with chronic liver diseases.*
9. *Reporting should include detail required for independent analysis of the quality of the test and ideally include; anatomical site of assessment, probe type, number of valid shots, median LSM, IQR and IQR/M, fasting status and ALT.*

TE in Chronic Hepatitis C (CHC)

The development of cirrhosis in patients with HCV infection is associated with poor outcome.[34] Furthermore there is strong data indicating that the degree of hepatic fibrosis can predict liver related endpoints[35] as well as being a factor used to identify patients requiring anti-viral therapy. Prior to April 2006, the importance of staging liver fibrosis to identify patients at risk of adverse outcome from HCV infection was reinforced by the Pharmaceutical Benefits Scheme which reimbursed the costs of therapy only in the setting of evidence of Metavir stage 2, 3 or 4 fibrosis (or equivalent index), or stage 1 fibrosis with grade A2 or A3 inflammation. This mandatory requirement was subsequently

removed. However an assessment of hepatic fibrosis remains paramount to the management of patients with CHC.

In recognition of this, the current EASL guidelines for the management of CHC[36] state that "Transient elastography (TE) can be used to assess liver fibrosis in patients with chronic hepatitis C". These guidelines go further and indicate that "the combination of blood tests or the combination of transient elastography and a blood test improve accuracy and reduce the necessity of using liver biopsy to resolve uncertainty".

Diagnostic Performance of Transient Elastography In HCV

Numerous studies have examined the performance of TE in the assessment of hepatic fibrosis in HCV infection.[14, 37-46] A consistent theme has emerged in that TE performs better for the detection of cirrhosis (AUROCs of 0.90-0.98 using a cut off of 11.9 kPa – 14.8 kPa) than significant (F≥2) hepatic fibrosis (AUROCs of 0.75-0.91 using a cutoff of 5.2 kPa – 8.8 kPa [See Table 1 and Table 2]). It is erroneous however to directly compare the results and "cut-offs" proposed by these studies due to significant variation in the prevalence of both significant fibrosis and cirrhosis across the cohorts. The fact that the identification of ≥F2 ("significant fibrosis") is a challenge for TE should not be a surprise considering the histological difference between F1 and F2 reflects location rather than the quantity of liver fibrosis.[24]

A recent review indicates that correct classification of patients with significant fibrosis (≥ F2) will occur in between 68% -83% of patients using a cut off of 7.1-8.6.[47] What is the clinical relevance of misclassifying F0-1 and ≥ F2? In a study of 300 patients with HCV, discordance between the identification of ≥ F2 by TE and liver biopsy was found in 34% of patients.[48] However, serious misclassification

occurred in only nine patients (3%) with advanced fibrosis as misclassified as F0-1. The remainders of misclassifications were between F1 and F2. The performance of TE may be improved when the IQR/Median is 0.21 rather than 0.3.[10]

Using TE to prognosticate in HCV

There is robust data to support the association between LSM and survival. A French study examining 5 year survival in a large cohort of HCV positive patients[25] demonstrated the overall survival (95% CI) using liver stiffness was for LSM ≤9.5 kPa: 96% (94%–98%); >9.5 kPa: 77% (72%–82%); >20 kPa: 66% (61%–71%); >30 kPa: 57% (50%–64%); >40 kPa: 47% (37%–57%); >50 kPa: 42% (29%–55%). TE may stratify the risk of HCC in patients with HCV infection.[28, 49] In a Japanese population, a LSM ranging between 10-15kPa, 15-20kPa and 20-25kPa and > 25kPa conferred a 17, 21, 26 and 45 fold relative risk for liver cancer compared to those with TE score below 10kPa.[28] In addition to predicting liver cancer, overall survival was also inversely correlated with increasing liver stiffness in HCV.[25, 50] Prospective studies and the applicability to different patient populations will be required in order to validate these findings. In a cross sectional study, cut-off values for the presence of oesophageal varices stage 2/3, cirrhosis Child-Pugh B or C, past history of ascites, hepatocellular carcinoma, and oesophageal variceal bleeding were 27.5, 37.5, 49.1, 53.7, and 62.7 kPa, respectively.[50] TE has been shown to predict the risk of complications of portal hypertension with a cut off of 21kPa to identify those at increased risk.[27, 51, 52] There is a reasonable correlation between HVPG and LSM[26] however there is no cut-off able to identify those with varices of a size that would benefit from primary prophylaxis. Therefore, as the present time, endoscopy screening

is still required.[1, 27, 51] There is emerging data suggesting that spleen stiffness or the LSPS score (Liver stiffness measure× Spleen diameter / Platelet ratio Score) may be useful in the assessment of portal hypertension and portal hypertensive complication.[53] Further work needs to be done before the role of TE in portal hypertension can be defined.

A recent study[54] provides the first solid evidence that serial assessments for liver stiffness over a three year may be able to stratify HCV patients into groups based on overall survival. Excellent survival with a liver related mortality / transplantation rate ≤ 1.2% over three years was observed in three groups of patients; (1) LSM ≤ 7 kPa regardless of response to antiviral therapy, (2) LSM ≥ 7 kPa with an SVR, (3) LSM 7-14 kPa with a change of LSM ≤ 1 kPa/year. This compares to liver-related mortality of 6.6-10.4% in patients with an LSM ≥ 14 kPa and no LSM increase over 3 years or LSM 7-14 kPa with a change of LSM ≥ 1 kPa/year. Not surprisingly the highest liver-related mortality (21.4%) was in the group with a baseline LSM ≥ 14 kPa and any increase of LSM over three years.

The combination of non-invasive tests may improve upon the performance of an individual test and overcome the shortcomings of any individual tests.[55] The combination of TE and biomarkers may improve the accuracy for diagnosing significant fibrosis, not necessarily cirrhosis.[40, 56, 57]

Limitations of Transient Elastography

The influence of hepatic necro-inflammation on LSM in HCV remains controversial with conflicting data within the literature.[37, 58-60] Nevertheless, the influence of ALT on TE scores in the setting of hepatitis B virus (HBV) infection are well accepted, and therefore should be kept in mind in the minority of patients with HCV who have marked ALT flares. A study by Tapper et al[60]

highlighted the impact of ALT on LSM in a population of HCV patients with biopsy proven F0-2 fibrosis. This is an important group of patients who are at risk of an overestimation of fibrosis according to TE, because of liver inflammation. In this study there was a strong relationship between ALT and the rates of overestimation of fibrosis stage according to established cut-offs. Using 12.5 kPa as the TE cut off for cirrhosis, patients with an ALT ≥ 80 IU/L were 3.5 times more likely to reach this threshold compared to those with an ALT ≤ 40 IU/L. This figure rose to 3.8 times if the ALT was ≥ 120 IU/L. In this setting approximately 25% of patients with F0-2 fibrosis have an LSM ≥ 12.5 kPa when the ALT ≥ 120 IU/L compared to only 5% with an ALT ≤ 40 IU/L. Therefore knowledge of the patients ALT level is important in the interpretation of TE results

It is conceivable that moderate to severe steatosis may also influence the TE score[61, 62] although this is an inconsistent finding, possibly explained by variation in study population.[3, 58, 63] Steatosis is not thought to affect the diagnosis of cirrhosis.[37]

Consensus Recommendations

1. *There is substantial data indicating TE provides additional information to the clinician that may assist in establishing treatment priorities and clinical decision making for the management of CHC provided that consideration is given to factors that may adversely affect its performance.*[36]
2. *For patients not undergoing a liver biopsy, TE or another validated non-invasive technique should be performed in all patients with HCV infection.*
3. *There is no data regarding the timing of repeat LSM assessments in individual patients although many groups currently perform TE every 1-2*

years for patients undergoing surveillance while awaiting CHC therapy. Data supporting ability of TE to reliably detect progression is limited to small studies.[64]

4. *For significant fibrosis (≥F2) the proposed existing cutoffs (6.8kPa-8.8kPa) have a high positive predictive value (83-97%) but variable negative predictive value (23-85%) and therefore a higher LSM is better at confirming the presence of ≥F2 rather than excluding it. There are many factors that limit TE ability to distinguish F1 from F2. These include limitations of liver biopsy itself particularly for this early stage of liver fibrosis.*
5. *For advanced fibrosis (≥ F3), a cutoff ranging from 8.9-10.8 kPa has a PPV and NPV of 71%-89% and 78%-95% respectively.*
6. *For cirrhosis the proposed existing cutoffs (11.9kPa-14.8kPa) offer a positive predictive value ranging from 52%-85%. Therefore an LSM above these cut offs may not, on its own be enough to confirm the presence of cirrhosis. These cutoffs are however associated with a high negative predictive value (≥95%) and therefore function well for the exclusion of cirrhosis.*
7. *Treatment decisions should not be solely based on LSM.*
8. *Current guidelines recommend avoiding response-guided therapy in genotype 1 patients with cirrhosis although there is no data regarding the use of TE assessment in the determination of CHC treatment duration. Therefore this decision needs to be individualized.*
9. *TE may overestimate the degree of hepatic fibrosis in patients with early stage disease and ALT elevation. The interpretation of TE should be made in*

conjunction with knowledge of the ALT and TE should be interpreted with caution in patients with a markedly elevated ALT.

10. *There is evidence suggesting that TE may improve the prognostic stratification of patients with cirrhosis beyond that offered by biopsy or Childs-Pugh /MELD score. Further longitudinal studies are required.*

TE in Chronic Hepatitis B (CHB)

In the past, histological examination of liver tissue has been an essential part of hepatitis B management. The mandatory requirement for liver biopsy prior to initiating antiviral therapy for CHB was removed from the PBS in 2011. Clinicians and patient advocate groups welcomed this change. The current Australian[65] and American guidelines[66] do not specifically address the use of LSM or other non-invasive technologies for the management of hepatitis B. However the more recent European[67] and the recently released UK focused NICE guidelines[68] have included routine assessment of LSM as part of the management algorithm for certain HBV patients. The EASL guidelines[67] do acknowledge the need for further research regarding the use on non-invasive markers for the assessment and follow-up of patients with HBV, however, concurrently state that "a non-invasive method for the estimation of the extent of fibrosis and most importantly to confirm or rule out cirrhosis is extremely useful in patients who start treatment without liver biopsy."

Diagnostic performance of transient elastography in HBV

TE has been most extensively studied in patients with hepatitis C. In comparison, relatively few studies are dedicated to LSM in subjects with HBV. There is ongoing debate whether the diagnostic performance of Transient Elastography

differs between these two diseases. Patrick Marcellin's group from Paris [38] directly compared the diagnostic performance of LSM in patients with chronic hepatitis B and chronic hepatitis C and found no difference in the area under the receiver-operating characteristic (AUROC) curves for predicting significant fibrosis (F≥2), advanced fibrosis (F≥3) and cirrhosis (F=4) in HCV and HBV patients (*P*=0.975, *P*=0.820, *P*=0.740 respectively).

Table 3 and Table 4 summarise the data from the most relevant studies analysing the diagnostic accuracy of LSM in HBV.

Limitations of TE

One limitation of TE is that the liver stiffness measurement increases with higher ALT levels regardless of the fibrosis staging. Chan et al [69] demonstrated that elevated ALT concentrations were associated with significantly higher LSM (OR 2.8, CI: 1.6-5.0, *P*<0.001) for any given fibrosis stage. Although the AUROCs in patients with bridging fibrosis and cirrhosis were not significantly different with elevated ALT, the authors proposed various optimal cut-offs depending on magnitude of ALT elevation (normal ALT or ALT>1-5 times ULN [ULN for ALT in this study was 56 IU/ml – personal communication from Dr H. Chan]). The proposed algorithm considered patients with a normal ALT and LSM between 6.0 and 9.0 kPa as being in a "grey zone" and suggested further evaluation with liver biopsy. Similarly patients with an elevated ALT (>1-5 x ULN) were considered in the grey zone if their LSM ranged between 7.5- 12.0 kPa. Marcellin et al [70] also confirmed a positive correlation on univariate analysis between LSM and both AST and ALT (Pearson's correlation coefficient, r=0.509, *P*<0.001; r=0.348, *P*<0.001) but importantly found a significant positive correlation between METAVIR activity grade (A) and LSM. Nevertheless, on multivariate

analysis, only METAVIR fibrosis stage (F) significantly correlated with LSM. Verveer et al [30] also demonstrated that hepatic inflammation assessed by hepatic necroinflammatory index (HAI, Ishak) increased liver stiffness regardless of fibrosis stage (P<0.001), and similarly, an increased ALT serum concentration was associated with increased LSM (P=0.002).[30]

Other author(s) have challenged the approach of using ALT-guided cut-offs. Cardoso et al,[38] in a single institution in Paris compared patients with HCV and HBV and although they demonstrated an overall positive correlation between ALT and LSM (r=0.365, P < 0.001) there were no significant differences in LSM for patients with either normal or elevated ALT in patients with either F0/F1 or F3/F4. The authors confirmed the Chan et al finding that variations in ALT did not result in significant differences in AUROCs for patients with advanced fibrosis and cirrhosis and concluded that in patients with HBV, ALT specific cut-offs did not enhance diagnostic performance.[38]

Monitoring of disease progression/regression in HBV

Numerous studies have now reported a reduction in LSM occurring after initiation of antiviral therapies. Vigano et al [71] examined 104 patients with HBV treated with entecavir for a median period of 11 months and noted a significant reduction in LSM from a mean of 10.0 kPa to 6.9 kPa (*P*<0.0001) whether or not ALT had normalised. Reduction in LSM occurred in both cirrhotic and non-cirrhotic subjects affirming the notion that cirrhosis may be partially reversible. Anderson et al [72] studied 53 patients with advanced fibrosis or cirrhosis (determined by either liver biopsy or clinical criteria) who were commenced on antiviral therapy for median treatment duration of 51 months. The cirrhotic patients all had LSM ≥ 11.0 kPa at study entry whereas after antiviral therapy

35% had LSM < 7.2, 12% had LSM 8.1-10.9 and 53% had LSM ≥11.0 kPa. A potential weakness of this and many other studies is the lack of repeat liver biopsy to provide histological evidence for regression of cirrhosis. A possible confounder to the apparent improvement in fibrosis is the reduction in LSM that occurs because of resolution of necroinflammatory activity that typically accompanies antiviral therapy.[73] Wong et al [74] prospectively studied 71 patients with chronic HBV, with paired biopsies before and after 48 weeks of antiviral therapy. Similar to other authors there was a demonstrated reduction in LSM, however the authors concluded that a decrease in LSM was an unreliable indicator of fibrosis regression.[74] Similarly, Lim et al [75] in 15 patients with paired liver biopsies reported a decrease in LSM that correlated significantly with improvement in necroinflammatory scores and not fibrosis stage.[75]

A more robust study by Fung et al [76] followed 426 patients with HBV of whom 110 received oral antiviral therapy for a period greater than 3 years. A significant decline in LSM was observed in patients with an elevated baseline ALT receiving oral antiviral therapy (7.8 kPa to 6.1 kPa, *P*=0.002). In patients with a normal ALT (defined as female ≤19 IU/L, male ≤30 IU/L) who were not treated with antiviral therapy, there was also an observed reduction in LSM over the study period (5.3 kPa to 4.9 kPa, *P*=0.005).[76]

Spontaneous hepatitis B flares and acute hepatitis B are known to result in transient increases in LSM. Oliveri et al studied 297 consecutive patients and showed that necroinflammatory scores and ALT levels were independently associated with LSM and in 80 treated patients in whom ALT had been elevated 1.2 to 4.4-fold the LSM paralleled the ALT decline following initiation of antiviral therapy.[77]

A particular subgroup that requires mention is the hepatitis B inactive carriers. These individuals are characterised by very low levels of viral replication, persistently normal ALT and a low risk of histological progression. Individuals in this phase of disease may not require anti-viral therapy. Several studies have included cohorts of patients with inactive hepatitis B[78-82]. These patients appear to have a low rate of LSM progression over time and a low rate of clinically relevant outcomes. In one of these cohorts[82], only 11 patients (5.5%) had an LSM >7.2kPa. The elevated LSM persisted over time in 2 patients both of whom underwent biopsies which indicted the presence of significant fibrosis (F2 and F3). TE may therefore be a useful tool, in conjunction with biochemical, virological and clinical assessments to monitor inactive carriers overtime and provide a mechanism for identifying patients most in need of liver biopsy[83].

Consensus Recommendations

1. *We recommend TE (or alternative non-invasive tests) as the initial investigation for determination of hepatic fibrosis in individuals with chronic hepatitis B not undergoing liver biopsy.*
2. *We recommend TE (or alternative non-invasive tests) for patients who start treatment without liver biopsy in order to establish a baseline LSM. As in HCV, TE has a higher NPV than PPV and is therefore better at excluding cirrhosis than confirming it.*
3. *Because an assessment of fibrosis is only one of several factors determining management decisions, treatment recommendations and follow-up, TE should be interpreted as part of specialist care and is not recommended for isolated use in primary health care to determine suitability for treatment or specialist referral.*

4. *In view of the relationship between elevated ALT associated with viral flares it would seem sensible to measure liver stiffness where practical, once the elevation of ALT has subsided. Testing of ALT around the time of LSM is therefore recommended.*
5. *Interpretation of Liver stiffness measurement in patients with elevated ALT should take into account that necroinflammation can contribute to stiffness and therefore result in an overestimation of fibrosis stage. The use of algorithms that incorporate ALT may mitigate against this.*

CONCLUSIONS

The absence of mandatory liver biopsies in the management of HBV and HCV has removed a significant barrier to treatment of these conditions but, in turn, has presented new challenges for the patient and clinician in the assessment of liver fibrosis related to these infections. In 2014, non-invasive assessment of liver fibrosis has become widely accepted as a clinically useful investigation in the assessment of patients with chronic liver diseases who have not or do not wish to have a liver biopsy as part of a formal histological assessment.

Regardless of the technique used to assess liver fibrosis (either liver biopsy or non-invasive tools such as TE) one must remain cognisant of the potential limitations and margin for error and incorrect staging. An assessment of liver fibrosis therefore should not become overly reliant on a single assessment but instead be used in a clinically appropriate manner and interpreted in conjunction with the clinical situation.

From a practical point-of-view, we use TE as the initial non-invasive tool in the assessment of patients with HCV and HBV in order to establish management

priorities. Where results are incongruous with the clinical situation or where the interpretation results in a significant deviation in clinical management, a second non-invasive tool or a liver biopsy would be a reasonable approach. There are no guidelines or evidence supporting the frequency with which this assessment should be performed. Although recent data from the HCV literature suggests the frequency of monitoring may be dependent on the baseline assessment. However where TE has been able to produce reliable and reproducible LSMs we are performing TE on a 1-2 yearly basis for the majority of our patients undergoing clinic follow up particularly in patients with a high baseline LSM or co-morbidities in order to identify and treat more aggressive disease. This remains an area that requires further clarification and will have economic implications.

The literature surrounding the use of non-invasive tools is rapidly evolving. It is hoped that future research will help to define the role TE and other non-invasive tools have in predicting patient outcomes such as HCC development, hepatic decompensation and survival. It is also likely that the merits of new or alternative techniques such as SWE and ARFI will become clearer with time.

[1] Castera L, Forns X, Alberti A. Non-invasive evaluation of liver fibrosis using transient elastography. *J Hepatol*. 2008; **48**: 835-47.
[2] de Ledinghen V, Vergniol J. Transient elastography for the diagnosis of liver fibrosis. *Expert Rev Med Devices*. 2010; **7**: 811-23.
[3] 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.
[4] Castera L, Foucher J, Bernard PH, *et al.* Pitfalls of liver stiffness measurement: a 5-year prospective study of 13,369 examinations. *Hepatology*. 2010; **51**: 828-35.
[5] Kettaneh A, Marcellin P, Douvin C, *et al.* Features associated with success rate and performance of FibroScan measurements for the diagnosis of cirrhosis in HCV patients: a prospective study of 935 patients. *J Hepatol*. 2007; **46**: 628-34.
[6] Kemp W, Roberts S. Feasibility and performance of the FibroScan XL probe. *Hepatology*. 2012; **55**: 1308-9; author reply 9-10.
[7] Myers RP, Pomier-Layrargues G, Kirsch R, *et al.* Feasibility and diagnostic performance of the fibroscan xl probe for liver stiffness measurement in overweight and obese patients. *Hepatology*. 2011.
[8] de Ledinghen V, Vergniol J, Foucher J, El-Hajbi F, Merrouche W, Rigalleau V. Feasibility of liver transient elastography with FibroScan using a new probe for obese patients. *Liver Int*. 2010; **30**: 1043-8.
[9] Myers RP, Crotty P, Pomier-Layrargues G, Ma M, Urbanski SJ, Elkashab M. Prevalence, risk factors and causes of discordance in fibrosis staging by transient elastography and liver biopsy. *Liver Int*. 2010.
[10] Lucidarme D, Foucher J, Le Bail B, *et al.* Factors of accuracy of transient elastography (fibroscan) for the diagnosis of liver fibrosis in chronic hepatitis C. *Hepatology*. 2009; **49**: 1083-9.
[11] Boursier J, Zarski JP, de Ledinghen V, *et al.* Determination of reliability criteria for liver stiffness evaluation by transient elastography. *Hepatology*. 2013; **57**: 1182-91.
[12] Boursier J, Konate A, Guilluy M, *et al.* Learning curve and interobserver reproducibility evaluation of liver stiffness measurement by transient elastography. *Eur J Gastroenterol Hepatol*. 2008; **20**: 693-701.
[13] 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.
[14] Degos F, Perez P, Roche B, *et al.* Diagnostic accuracy of FibroScan and comparison to liver fibrosis biomarkers in chronic viral hepatitis: a multicenter prospective study (the FIBROSTIC study). *J Hepatol*. 2010; **53**: 1013-21.
[15] Arena U, Lupsor Platon M, Stasi C, *et al.* Liver stiffness is influenced by a standardized meal in patients with chronic hepatitis C virus at different stages of fibrotic evolution. *Hepatology*. 2013; **58**: 65-72.
[16] Berzigotti A, De Gottardi A, Vukotic R, *et al.* Effect of meal ingestion on liver stiffness in patients with cirrhosis and portal hypertension. *PLoS One*. 2013; **8**: e58742.

[17] Mederacke I, Wursthorn K, Kirschner J, *et al.* Food intake increases liver stiffness in patients with chronic or resolved hepatitis C virus infection. *Liver Int*. 2009; **29**: 1500-6.
[18] Bedossa P, Carrat F. Liver biopsy: the best, not the gold standard. *J Hepatol*. 2009; **50**: 1-3.
[19] 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.
[20] Bedossa P. Assessment of hepatitis C: non-invasive fibrosis markers and/or liver biopsy. *Liver Int*. 2009; **29 Suppl 1**: 19-22.
[21] Westin J, Lagging LM, Wejstal R, Norkrans G, Dhillon AP. Interobserver study of liver histopathology using the Ishak score in patients with chronic hepatitis C virus infection. *Liver*. 1999; **19**: 183-7.
[22] Bedossa P, Dargere D, Paradis V. Sampling variability of liver fibrosis in chronic hepatitis C. *Hepatology*. 2003; **38**: 1449-57.
[23] Mehta SH, Lau B, Afdhal NH, Thomas DL. Exceeding the limits of liver histology markers. *J Hepatol*. 2009; **50**: 36-41.
[24] Standish RA, Cholongitas E, Dhillon A, Burroughs AK, Dhillon AP. An appraisal of the histopathological assessment of liver fibrosis. *Gut*. 2006; **55**: 569-78.
[25] 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**: 1970-9, 9 e1-3.
[26] Vizzutti F, Arena U, Romanelli RG, *et al.* Liver stiffness measurement predicts severe portal hypertension in patients with HCV-related cirrhosis. *Hepatology*. 2007; **45**: 1290-7.
[27] Robic MA, Procopet B, Metivier S, *et al.* Liver stiffness accurately predicts portal hypertension related complications in patients with chronic liver disease: a prospective study. *J Hepatol*. 2011; **55**: 1017-24.
[28] Masuzaki R, Tateishi R, Yoshida H, *et al.* Prospective risk assessment for hepatocellular carcinoma development in patients with chronic hepatitis C by transient elastography. *Hepatology*. 2009; **49**: 1954-61.
[29] Jung KS, Kim SU, Ahn SH, *et al.* Risk assessment of hepatitis B virus-related hepatocellular carcinoma development using liver stiffness measurement (FibroScan). *Hepatology*. 2010.
[30] Verveer C, Zondervan PE, ten Kate FJ, Hansen BE, Janssen HL, de Knegt RJ. Evaluation of transient elastography for fibrosis assessment compared with large biopsies in chronic hepatitis B and C. *Liver Int*. 2012; **32**: 622-8.
[31] Tsochatzis EA, Gurusamy KS, Ntaoula S, Cholongitas E, Davidson BR, Burroughs AK. Elastography for the diagnosis of severity of fibrosis in chronic liver disease: a meta-analysis of diagnostic accuracy. *J Hepatol*. 2011; **54**: 650-9.
[32] Arena U, Vizzutti F, Corti G, *et al.* Acute viral hepatitis increases liver stiffness values measured by transient elastography. *Hepatology*. 2008; **47**: 380-4.
[33] Millonig G, Reimann FM, Friedrich S, *et al.* Extrahepatic cholestasis increases liver stiffness (FibroScan) irrespective of fibrosis. *Hepatology*. 2008; **48**: 1718-23.

[34] Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. *Lancet*. 1997; **349**: 825-32.
[35] Everhart JE, Wright EC, Goodman ZD, *et al.* Prognostic value of Ishak fibrosis stage: findings from the hepatitis C antiviral long-term treatment against cirrhosis trial. *Hepatology*. 2010; **51**: 585-94.
[36] EASL Clinical Practice Guidelines: management of hepatitis C virus infection. *J Hepatol*. 2011; **55**: 245-64.
[37] 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.
[38] Cardoso AC, Carvalho-Filho RJ, Stern C, *et al.* Direct comparison of diagnostic performance of transient elastography in patients with chronic hepatitis B and chronic hepatitis C. *Liver Int*. 2012; **32**: 612-21.
[39] Castera L. Transient elastography and other noninvasive tests to assess hepatic fibrosis in patients with viral hepatitis. *J Viral Hepat*. 2009; **16**: 300-14.
[40] 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.
[41] Cross TJ, Calvaruso V, Maimone S, *et al.* Prospective comparison of Fibroscan, King's score and liver biopsy for the assessment of cirrhosis in chronic hepatitis C infection. *J Viral Hepat*. 2010; **17**: 546-54.
[42] Lupsor M, Badea R, Stefanescu H, *et al.* Analysis of histopathological changes that influence liver stiffness in chronic hepatitis C. Results from a cohort of 324 patients. *J Gastrointestin Liver Dis*. 2008; **17**: 155-63.
[43] Lupsor Platon M, Stefanescu H, Feier D, Maniu A, Badea R. Performance of unidimensional transient elastography in staging chronic hepatitis C. Results from a cohort of 1,202 biopsied patients from one single center. *J Gastrointestin Liver Dis*. 2013; **22**: 157-66.
[44] Sporea I, Sirli R, Deleanu A, *et al.* Liver stiffness measurements in patients with HBV vs HCV chronic hepatitis: a comparative study. *World J Gastroenterol*. 2010; **16**: 4832-7.
[45] Zarski JP, Sturm N, Guechot J, *et al.* Comparison of nine blood tests and transient elastography for liver fibrosis in chronic hepatitis C: the ANRS HCEP-23 study. *J Hepatol*. 2012; **56**: 55-62.
[46] Ziol M, Handra-Luca A, Kettaneh A, *et al.* Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with chronic hepatitis C. *Hepatology*. 2005; **41**: 48-54.
[47] Castera L. Noninvasive methods to assess liver disease in patients with hepatitis B or C. *Gastroenterology*. 2012; **142**: 1293-302 e4.
[48] Calvaruso V, Camma C, Di Marco V, *et al.* Fibrosis staging in chronic hepatitis C: analysis of discordance between transient elastography and liver biopsy. *J Viral Hepat*. 2010; **17**: 469-74.
[49] Wang HM, Hung CH, Lu SN, *et al.* Liver stiffness measurement as an alternative to fibrotic stage in risk assessment of hepatocellular carcinoma incidence for chronic hepatitis C patients. *Liver Int*. 2013; **33**: 756-61.
[50] Foucher J, Chanteloup E, Vergniol J, *et al.* Diagnosis of cirrhosis by transient elastography (FibroScan): a prospective study. *Gut*. 2006; **55**: 403-8.

[51] 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**: 1261-8.
[52] Lemoine M, Katsahian S, Ziol M, *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**: 1102-10.
[53] Colecchia A, Montrone L, Scaioli E, *et al.* Measurement of spleen stiffness to evaluate portal hypertension and the presence of esophageal varices in patients with HCV-related cirrhosis. *Gastroenterology*. 2012; **143**: 646-54.
[54] Vergniol J, Boursier J, Coutzac C, *et al.* The evolution of non-invasive tests of liver fibrosis is associated with prognosis in patients with chronic hepatitis C. *Hepatology*. 2014.
[55] Castera L, Sebastiani G, Le Bail B, de Ledinghen 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**: 191-8.
[56] Boursier J, Vergniol J, Sawadogo A, *et al.* The combination of a blood test and Fibroscan improves the non-invasive diagnosis of liver fibrosis. *Liver Int*. 2009; **29**: 1507-15.
[57] Poynard T, Vergniol J, Ngo Y, *et al.* Staging chronic hepatitis C in seven categories using fibrosis biomarker (FibroTest) and transient elastography (FibroScan(R)). *J Hepatol*. 2014; **60**: 706-14.
[58] Fraquelli M, Rigamonti C, Casazza G, *et al.* Etiology-related determinants of liver stiffness values in chronic viral hepatitis B or C. *J Hepatol*. 2011; **54**: 621-8.
[59] Scott DR, Levy MT. Liver transient elastography (Fibroscan): a place in the management algorithms of chronic viral hepatitis. *Antivir Ther*. 2010; **15**: 1-11.
[60] Tapper EB, Cohen EB, Patel K, *et al.* Levels of alanine aminotransferase confound use of transient elastography to diagnose fibrosis in patients with chronic hepatitis C virus infection. *Clin Gastroenterol Hepatol*. 2012; **10**: 932-7 e1.
[61] Boursier J, de Ledinghen V, Sturm N, *et al.* Precise evaluation of liver histology by computerized morphometry shows that steatosis influences liver stiffness measured by transient elastography in chronic hepatitis C. *J Gastroenterol*. 2013.
[62] Sanchez-Conde M, Montes Ramirez ML, Bellon Cano JM, *et al.* Impact of liver steatosis on the correlation between liver stiffness and fibrosis measured by transient elastography in patients coinfected with human immunodeficiency virus and hepatitis C virus. *J Viral Hepat*. 2011; **18**: e278-83.
[63] Sanchez-Conde M, Miralles P, Bellon JM, *et al.* Use of transient elastography (FibroScan(R)) for the noninvasive assessment of portal hypertension in HIV/HCV-coinfected patients. *J Viral Hepat*. 2011; **18**: 685-91.
[64] Colletta C, Smirne C, Fabris C, *et al.* Value of two noninvasive methods to detect progression of fibrosis among HCV carriers with normal aminotransferases. *Hepatology*. 2005; **42**: 838-45.
[65] GESA. Clinical Update: Chronic Hepatitis B (CHB) Recommendations. 2010.
[66] Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology*. 2009; **50**: 661-2.

[67] EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. *J Hepatol*. 2012; **57**: 167-85.
[68] Sarri G, Westby M, Bermingham S, Hill-Cawthorne G, Thomas H. Diagnosis and management of chronic hepatitis B in children, young people, and adults: summary of NICE guidance. *Bmj*. 2013; **346**: f3893.
[69] Chan 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**: 36-44.
[70] 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**: 242-7.
[71] Vigano M, Massironi S, Lampertico P, *et al.* Changes in liver stiffness during entecavir therapy in patients with chronic hepatitis B. 2010; **50**: S145.
[72] Andersen ES, Weiland O, Leutscher P, *et al.* Low liver stiffness among cirrhotic patients with hepatitis B after prolonged treatment with nucleoside analogs. *Scandinavian journal of gastroenterology*. 2011; **46**: 760-6.
[73] Kim BK, Fung J, Yuen MF, Kim SU. Clinical application of liver stiffness measurement using transient elastography in chronic liver disease from longitudinal perspectives. *World J Gastroenterol*. 2013; **19**: 1890-900.
[74] Wong GL, Wong VW, Choi PC, *et al.* On-treatment monitoring of liver fibrosis with transient elastography in chronic hepatitis B patients. *Antiviral therapy*. 2011; **16**: 165-72.
[75] Lim SG, Cho SW, Lee YC, *et al.* Changes in liver stiffness measurement during antiviral therapy in patients with chronic hepatitis B. *Hepato-gastroenterology*. 2011; **58**: 539-45.
[76] 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. *Journal of viral hepatitis*. 2011; **18**: e200-5.
[77] Oliveri F, Coco B, Ciccorossi P, *et al.* Liver stiffness in the hepatitis B virus carrier: a non-invasive marker of liver disease influenced by the pattern of transaminases. *World J Gastroenterol*. 2008; **14**: 6154-62.
[78] Papatheodoridis GV, Manolakopoulos S, Margariti A, *et al.* The usefulness of transient elastography in the assessment of patients with HBeAg-negative chronic hepatitis B virus infection. *J Viral Hepat*. 2014; **21**: 517-24.
[79] Poynard T, Vergniol J, Ngo Y, *et al.* Staging chronic hepatitis B into seven categories, defining inactive carriers and assessing treatment impact using a fibrosis biomarker (FibroTest(R)) and elastography (FibroScan(R)). *J Hepatol*. 2014.
[80] Assal A, Mackie D, Cooper CL. Transient elastography, APRI, and ultrasound have minimal utility in chronic low-replicative hepatitis B infection. *Eur J Gastroenterol Hepatol*. 2014; **26**: 1010-4.
[81] Wong GL, Chan HL, Yu Z, Chan HY, Tse CH, Wong VW. Liver fibrosis progression is uncommon in patients with inactive chronic hepatitis B: a prospective cohort study with paired transient elastography examination. *J Gastroenterol Hepatol*. 2013; **28**: 1842-8.
[82] Castera L, Bernard PH, Le Bail B, *et al.* Transient elastography and biomarkers for liver fibrosis assessment and follow-up of inactive hepatitis B carriers. *Aliment Pharmacol Ther*. 2011; **33**: 455-65.

[83] Castera L. Hepatitis B: are non-invasive markers of liver fibrosis reliable? *Liver Int*. 2014; **34 Suppl 1**: 91-6.
[84] 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.
[85] Vigano M, Paggi S, Lampertico P, *et al.* Dual cut-off transient elastography to assess liver fibrosis in chronic hepatitis B: a cohort study with internal validation. *Alimentary pharmacology & therapeutics*. 2011; **34**: 353-62.
[86] Lesmana CR, Salim S, Hasan I, *et al.* Diagnostic accuracy of transient elastography (FibroScan) versus the aspartate transaminase to platelet ratio index in assessing liver fibrosis in chronic hepatitis B: the role in primary care setting. *Journal of clinical pathology*. 2011; **64**: 916-20.
[87] Kim do Y, Kim SU, Ahn SH, *et al.* Usefulness of FibroScan for detection of early compensated liver cirrhosis in chronic hepatitis B. *Dig Dis Sci*. 2009; **54**: 1758-63.

Figure 1. Prediction of fibrosis score by Liver Stiffness Measure (LSM). The sum of the predictions for a particular LSM value = 100%.

Table 1: Performance of Transient Elastography for the detection of significant fibrosis (≥ F2) compared to liver biopsy in chronic hepatitis C.

Author	Patients	≥ F2 (%)	Cutoffs (kPa)	AUROC	Se (%)	Sp (%)	PPV	NPV	+LR	-LR
Castera 2005[40]	183	74	7.1	0.83	67	89	95	48	6.1	0.4
Ziol 2005[46]	251	65	8.8	0.79	56	91	88	56	6.6	0.5
Lupsor 2008[42]	324	65	7.4	0.86	76	84	90	85	4.6	0.3
Arena 2008[37]	150	56	7.8	0.91	83	82	83	79	4.6	0.2
Cross 2010[41]	187	48	6.75	0.86	68	91	96	49	7.6	0.6
Sporea 2010[44]	317	88	6.8	0.75	60	88	97	23		
Degos 2010[14]	913	62	5.2	0.75	90	32	68	66	1.3	0.3
Zarski 2012[45]	382	47	5.2	0.82	97	35	56	92		
Cardoso 2012[38]	363	54	7.1	0.87	68	89	88	70	6	0.35
Platon 2013[43]	1202	65	7.4	0.89	80	84	90	70	5	0.23

Se, Sensitivity; Sp, Specificity; PPV, Positive Predictive Value; NPV, Negative Predictive Value; LR, Likelihood ratio.

Table 2: Performance of Transient Elastography for the detection of cirrhosis (F4) compared to liver biopsy in chronic hepatitis C.

Author	Patients	Cirrhosis (%)	Cutoffs (kPa)	AUROC	Se (%)	Sp (%)	PPV	NPV	+LR	-LR
Castera 2005[40]	183	25	12.5	0.95	87	91	77	95	9.7	0.1
Ziol 2005[46]	251	19	14.6	0.97	86	96	78	97	23.1	0.1
Lupsor 2008[42]	324	21	11.9	0.94	87	91	72	96	9.7	0.1
Arena 2008[37]	150	19	14.8	0.98	94	92	73	98	11.3	0.1
Castera 2009[84]	298	23	12.5	0.96	83	95	85	95	16.6	0.2
Cross 2010[41]	187	27	10.1	0.97	93	88	68	98	7.4	0.07
Sporea 2010[44]	317	12	13.3	0.93	77	93	61	96		
Degos 2010[14]	913	14	12.9	0.9	72	89	52	95	6.8	0.3
Zarski 2012[45]	382	14	12.9	0.93	77	90	56	96		
Cardoso 2012[38]	363	9	12.5	0.95	84	94	58	98	14.7	0.17
Platon 2013[43]	1202	31	13.2	0.97	94	93	87	97	14	0.07

Se, Sensitivity; Sp, Specificity; PPV, Positive Predictive Value; NPV, Negative Predictive Value; LR, Likelihood ratio.

Table 3: Performance of Transient Elastography for the detection of significant fibrosis (≥ F2) compared to liver biopsy in chronic hepatitis B.

Author	Patients	≥ F2 (%)	Cutoff (kPa)	AUROC	Se (%)	Sp (%)	PPV	NPV	LR+	-LR
Degos 2010[14]	284	41.6%	5.2	0.75	89.0	38.0	50	82.9	1.43	0.29
Marcellin 2009[70]	173	50.3%	7.2	0.81	70	83	80	73	4.1	0.36
Cardoso 2012[38]	202	42.0%	7.2	0.87	74	88	82	82	6.20	0.30
Vigano 2011[85]	217	47.2%	8.7	0.85	64	92	86	69	7.5	0.40
			6.2		94	46	66†	87	1.7	0.10
			9.4		55	95	92	65	11	0.5
Oliveri 2008[77]	297	26 % (S≥3)	7.5	0.97	94	88.5	76.7	97.3	8.18	0.07
Lesmana‡ 2011[86]	117	62.4% (F≥2)	5.85	0.719	60.3	63.6	73.3	49.1	1.66	0.62
		23.9% (F≥3)	7.00	0.867	65.5	80.7	52.8	87.7	3.39	0.43
Verveer 2012[30]	125	53.5% (F≥2)	6.0	0.85	NR	NR	NR	NR	NR	NR
		27.8% (F≥3)	9.0	0.91	NR	NR	NR	NR	NR	NR

Se, Sensitivity; Sp, Specificity; PPV, Positive Predictive Value; NPV, Negative Predictive Value; LR, Likelihood ratio; NR, Not reported.

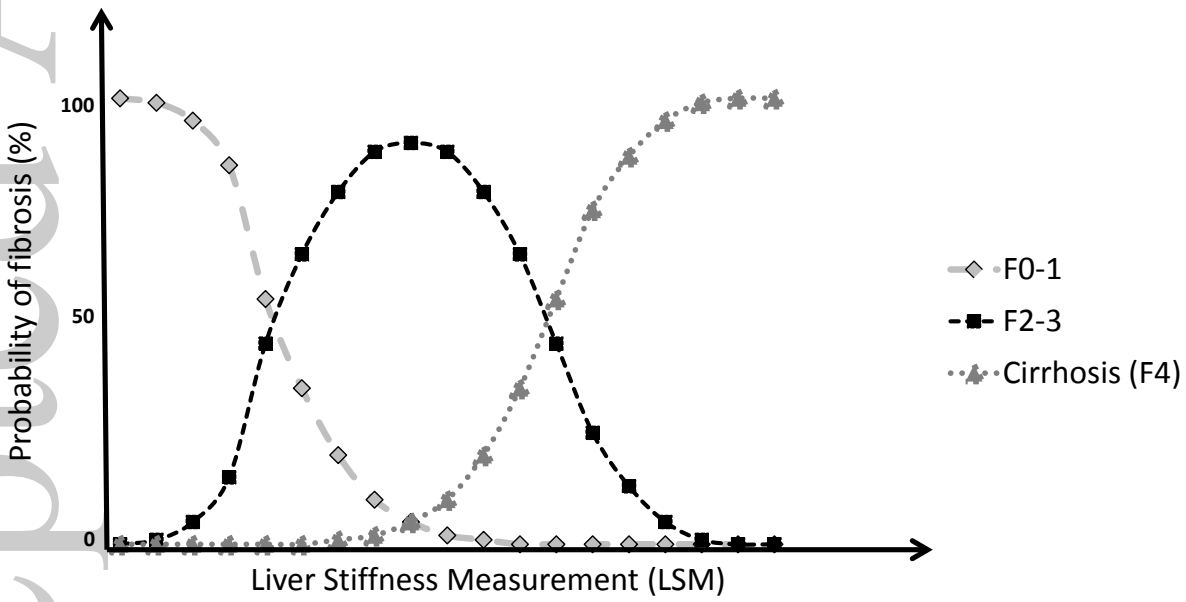
† The authors may have made an error with their notation. They discuss a cut-off to exclude significant fibrosis of <6.2 kPa and state that with a value < 6.2 kpa 62/66 patients are correctly classified. However, 59 patients in the group had <F2 and 66 patients had ≥F2. It is assumed that they meant >6.2 Kpa 62/66 were correctly classified.

‡ Community setting (selected patients who were intending to start antiviral therapy).

Table 4: Performance of Transient Elastography for the detection of cirrhosis (F4) compared to liver biopsy in chronic hepatitis B.

Author	Patients	Cirrhosis (%)	Cutoff (kPa)	AUROC	Se (%)	Sp (%)	PPV	NPV	+LR	-LR
Degos 2010[14]	284	10.2%	10.2	0.85	51.7	92.9	45.5	94.4	7.33	0.52
Marcellin 2009[70]	173	8.1%	11.0	0.93	93	87	38	99	7.0	0.08
Chan 2009[69] ALT < ULN	58	26%	9.0	0.96	100	88	75	100	8.6	0
Chan 2009[69] ALT >1-5 xULN	98	25%	12.0	0.94	79	92	76	93	9.8	0.23
Kim 2009[87]	91	42.9%	10.3	0.80	59	78	68	72	2.7	0.53
Cardoso 2012[38]	202	8%	11.0	0.94	75	90	39	98	7.34	0.28
Vigano 2011[85]	217	20%	9.4	0.94	100	82	51.2	100	5.5	0.00
			13.1	0.90	75	93	68.2	94	11.2	0.3
Oliveri 2008[77]	297	20%	11.8	0.97	86.5	96.3	86.5	96.3	23.2	0.14
Verveer 2012[30]	125	6.4%	13.0	0.90	NR	NR	NR	NR	NR	NR

Se, Sensitivity; Sp, Specificity; PPV, Positive Predictive Value; NPV, Negative Predictive Value; LR, Likelihood ratio; ALT, Alanine Aminotransferase; ULN, Upper limit of normal; NR, Not reported.



jgh_12865_f1.pdf