Hepatol Int (2011) 5:868–875
DOI 10.1007/s12072-011-9288-5

REVIEW ARTICLE

The use of transient elastography in the management of chronic hepatitis B

James Fung · Ching-Lung Lai · Wai-Kay Seto · Man-Fung Yuen

Received: 24 February 2011 / Accepted: 9 June 2011 / Published online: 22 June 2011

Abstract There has been increasing interest in noninvasive methods of assessing liver fibrosis over the last decade. The use of transient elastography in measuring liver stiffness has become the forefront of a wide range of noninvasive tools. Most of the other methods are based on measurements of biomarkers associated with fibrosis. There are several reasons for its wide acceptance, including the ease of performing a scan, the short procedure time, the results being immediately available on completion of the examination, and its reproducibility. For chronic hepatitis B (CHB), the cut-off values for F3 and F4 fibrosis range between 7.5–12.0 and 11.0–13.4 kPa, respectively, although the cut-offs may be slightly lower in those with normal ALT. In addition to measuring liver fibrosis, recent studies have demonstrated several other roles for transient elastography, including selecting patients who will benefit from antiviral therapy, monitoring response to antiviral therapy, and predicting long-term outcomes. However, there are limitations associated with transient elastography, including the confounding effects of inflammatory activity, and to a lesser extent, steatosis, on liver stiffness. There is also reduced accuracy observed in lower fibrosis stages (F0–F2). Furthermore, the incidences of failed and unreliable scan have been reported to be $\sim$ 3 and 16%, respectively. Although liver biopsy can be avoided in an estimated 50–60% using transient elastography, in situations where liver stiffness measurement is nondiagnostic or inconsistent with the clinical picture, a biopsy is still recommended. Further studies are needed to consolidate the role of transient elastography in the management of CHB, and for incorporation of this method into current treatment guidelines.

Keywords Noninvasive · Liver fibrosis · Fibroscan

J. Fung · C.-L. Lai · W.-K. Seto · M.-F. Yuen (✉)
Department of Medicine, Queen Mary Hospital,
The University of Hong Kong, 102 Pokfulam Road,
Hong Kong SAR, China
e-mail: mfyuen@hkucc.hku.hk

Introduction

An estimated 400 million people worldwide are chronically infected with the hepatitis B virus (HBV), with the majority located in the Asia Pacific and sub-Saharan region. HBV infection constitutes a significant health burden, with up to 40% chronically infected patients developing complications of liver disease, including cirrhosis and hepatocellular carcinoma (HCC) [1, 2]. In patients with chronic hepatitis B (CHB) infection, determination of the severity of liver fibrosis is particularly important for several reasons. First, the degree of fibrosis has prognostic significance. Second, it helps to identify patients who are likely to have the most benefit from antiviral therapy. Third, for those patients who are already receiving treatment, assessment of liver fibrosis may be helpful in determining their response to therapy. Finally, HCC and variceal screening should be implemented for patients identified with cirrhosis.

Currently, percutaneous liver biopsy is the most commonly used method for assessing liver fibrosis, and remains the gold standard, despite the limitations associated with inadequate specimen size and sampling error [3, 4]. The interpretation of liver histology is also subjected to both intra- and inter-observer variability, leading to erroneous staging of fibrosis. In addition, liver biopsy is an invasive procedure which can be associated with significant morbidity (and occasional mortality), rendering it less

acceptable by patients [5–7]. The latter reason is the strongest driving factor for the development of noninvasive methods to assess liver fibrosis.

Transient elastography using Fibroscan (Echosens, Paris, France) is now available in many countries since its development in 2003, and has become one of the leading noninvasive methods to determine liver fibrosis. The measurement of liver stiffness is based on the principle that an increase in liver fibrosis is proportional to a higher liver stiffness. The Fibroscan consists of a probe with an ultrasound transducer mounted on the axis of a vibrating piston. A piston is used to create a mechanical wave of low frequency and amplitude, creating a shear wave that is propagated through the liver tissue. The ultrasound transducer, which is located at the tip of the probe, is then used to map out the mechanical perturbation that was induced by the vibrating piston. The velocity of the shear wave can then be calculated, with higher shear wave velocity corresponding to higher liver stiffness, which corresponds to a higher stage of fibrosis. The liver stiffness value obtained from transient elastography ranges from a minimum of 2.5 kPa to a maximum reading of 75.0 kPa.

The popularity of transient elastography stems not only from its noninvasive nature and the absence of adverse effects, but also from the fact that the investigation can be rapidly performed, with an average procedure time of $\sim$5 min. Furthermore, the results are immediately available at the time of completion of the examination. Another advantage is that transient elastography can be easily learned within a short training period with highly reproducible results [8]. The current review will focus on the role of transient elastography in patients with CHB, highlighting the current and potential clinical applications and the limitations associated with liver stiffness measurement (LSM).

Assessment of liver fibrosis

The current primary indication for performing transient elastography is for the assessment of liver fibrosis to guide the treatment decisions. Most of the initial studies on LSMs have been performed in Caucasian patients with chronic hepatitis C, and there are abundant data validating the accuracy of transient elastography in this setting [9–11]. Since then, there have been many studies on the use of LSM in other liver diseases, including primary biliary cirrhosis, nonalcoholic fatty liver disease, and CHB [12–16]. Several meta-analyses performed recently have confirmed the accuracy of LSM in predicting significant liver fibrosis [17, 18]. In a meta-analysis of 50 studies, the mean area under receiver operating characteristics curve (AUROC) for the diagnosis of significant fibrosis, severe fibrosis, and cirrhosis was 0.84, 0.89, and 0.94, respectively [17].

One of the important aspects of interpreting liver stiffness results is the cut-off values that are adopted for the different stages of fibrosis, with higher cut-off levels corresponding to a higher fibrosis stage. These cut-off values have been derived from individual validation studies, and therefore are dependent on the population of patients that were recruited for those studies. Furthermore, the cut-off values are disease specific, with different values used for different disease etiologies. It is therefore important to adopt the values that are relevant to the disease and ethnic group as there are considerable differences. The reason for the difference in cut-off values between different diseases is not known, although the distribution of fibrous material is dependent on the origin of liver injury, which in turn is dependent on the underlying pathology. For example, the cirrhosis arising from CHB is often macronodular, and the pattern of nodule distribution and fibrous deposition may affect the liver stiffness. Another example is the centrizonal fibrosis of alcoholic liver disease, resulting in micronodular cirrhosis.

Validation studies in CHB

In an early validation study of 173 patients with CHB from five French hospitals, the performance of transient elastography was shown to be comparable with the results observed in patients with chronic hepatitis C. The AUROC for $F \geq 2$, $F \geq 3$, and $F = 4$ were 0.81, 0.93, and 0.93, respectively, with optimal cut-off liver stiffness values of 7.2, 8.1, and 11.0 kPa, respectively [15]. A similar cut-off value of 10.3 kPa for cirrhosis was obtained from a Korean study [19]. In another study of 161 Chinese patients with CHB from Hong Kong, the AUROC for $F \geq 3$ and $F = 4$ were 0.87 and 0.93, with an optimal cut-off value of 9.0 kPa for diagnosing liver cirrhosis [16]. Those with elevated alanine aminotransferase (ALT) had higher optimal cut-off levels compared to those with normal levels. A study of 188 CHB patients from Italy identified an optimal cut-off value of 7.5 and 11.8 kPa for S ≥ 3 and cirrhosis, respectively [20]. The optimal cut-off values for significant fibrosis and cirrhosis in patients with CHB are summarized in Table 1.

However, there are limitations associated with validation studies. Although liver biopsy is the current "gold" standard for assessing liver fibrosis, it is an imperfect benchmark. Sampling error remains one of the important limitations of liver biopsy, with size, length, and number of samples obtained being contributing factors. Therefore validation studies using liver biopsy as a reference will also be subjected to these limitations. Other factors which may affect the accuracy of validation studies include the unequal distribution of fibrosis stages in the study cohorts, the lack of concurrent biopsies and liver stiffness

Table 1 Optimal cut-off levels of significant fibrosis ($F \geq 2$/ $S \geq 3$) and cirrhosis in patients with CHB

Parameters	Marcellin et al. [15]	Oliveri et al. [20]	Chan et al. [16]		Kim et al. [19]
			Normal ALT	High ALT	
Number	173	188	58	98	91
Ethnicity	French	Italian	Chinese	Chinese	Korean
F ≥ 2/S ≥ 3					
Cut-off (kPa)	7.2	7.5	–	–	–
Sensitivity	70	93	–	–	–
Specificity	83	83	–	–	–
PPV	80	77	–	–	–
NPV	73	97	–	–	–
LR (+)	4.1	8.2	–	–	–
LR (−)	0.36	0.07	–	–	–
Cirrhosis					
Cut-off	11.0	11.8	9.0	13.4	10.3
Sensitivity	93	86	100	75	59
Specificity	87	96	88	93	78
PPV	38	87	75	78	68
NPV	99	96	100	92	72
LR (+)	7.1	23.1	8.6	11.1	2.7
LR (−)	0.08	0.14	0	0.27	0.53

PPV positive predicitive value, *NPV* negative predictive value, *LR* (+) positive likelihood ratio, *LR* (−) negative likelihood ratio

evaluations, and the lack of predefined quality criteria for biopsy specimens.

Normal liver stiffness

In addition to diagnosing patients with significant fibrosis and cirrhosis, it is also important to identify patients with normal liver or those with minimal fibrosis by having a cut-off value which defines normal liver stiffness. In a study of 429 healthy subjects, the mean liver stiffness was 5.49 ± 1.59 kPa, with slightly higher values in males compared with females (5.81 vs. 5.32 kPa, respectively, $p = 0.0002$) and in subjects with higher body mass index (BMI) >30 compared with BMI ≤30 (6.26 vs. 5.33 kPa, respectively, $p < 0.0001$) [21]. A mean liver stiffness of 4.8 ± 1.3 kPa was described in another study of 152 normal subjects from Romania, with a lower value observed in females compared with males (4.6 vs. 5.1 kPa, respectively, $p = 0.0082$) [22]. In a study of 602 blood donors from Italy, the median liver stiffness was 4.4 kPa [23]. The normal liver stiffness in Asian subjects appears to be comparable. A study of 69 healthy living liver and kidney donors admitted for transplantation in Korea showed a liver stiffness range of 3.9–5.3 kPa [24]. In another study of 28 Chinese living liver donors, the median liver stiffness was 4.6 kPa with all subjects having values of <7.2 kPa [25]. This cut-off value is lower than the cut-off value used for significant fibrosis without an overlap.

Indications for transient elastography in CHB

Apart from the assessment of liver fibrosis, LSM may also have other clinical applications. In patients with CHB, transient elastography may be helpful in selecting patients for antiviral therapy and predicting outcome of HBV infection.

Determining the phase of infection

The natural history of CHB infection can be described in four phases, namely the immunotolerant phase, immune clearance phase, quiescent phase, and the reactivation phase [26]. The clinical relevance of the different phases is predominantly to determine whether there is underlying significant disease activity to warrant antiviral therapy.

For hepatitis B e-antigen (HBeAg)-positive patients, it is important to identify those who are in the immune-clearance phase so that antiviral therapy can be considered for those with significant disease activity. At present there is no reliable marker to accurately indicate the transition from immunotolerance to the immune clearance phase. The HBV DNA levels are not useful in HBeAg-positive patients as patients in the immune tolerant phase have very high viral load, but have minimal or absent disease activity [27]. Although higher ALT levels have shown to be associated with increased risk of fibrosis and cirrhosis [28, 29], using ALT as a surrogate marker for transition into the immune clearance phase may not be reliable as a

significant proportion of patients with significant disease activity have normal ALT levels [28, 30–32]. Transient elastography has a potential role not only in identifying patients in the "immune clearance phase" with normal ALT, but also in identifying those with elevated liver stiffness, which may indicate underlying disease activity or established fibrosis. Studies are required to determine the usefulness of LSM in this unexplored role.

For HBeAg-negative patients, various studies have shown that multiple factors including older age, low platelet count, male gender, and higher ALT levels are associated with increased severity of fibrosis [28, 29, 33–36]. Transient elastography may also have a role in distinguishing patients who are inactive carriers from those who have ongoing disease activity. In a study of 220 HBeAg-negative CHB patients, of which 95 had persistent or intermittent elevation of ALT and/or HBV DNA $>10^5$ copies/mL, there was a significantly higher mean liver stiffness compared to those who were inactive carriers (8.53 vs. 4.83 kPa, respectively, $p < 0.001$) [37]. A study of 68 inactive carriers showed a mean liver stiffness value of 5.0 kPa [20]. In another recent study of 329 HBeAg-negative patients, the liver stiffness was significantly lower in inactive carriers compared to those with active hepatitis (4.8 vs. 6.8 kPa, $p < 0.0001$) [38]. A cut-off value of 5.0 kPa may be useful in HBeAg-negative patients to identify those with underlying activity or significant fibrosis despite having ALT levels within the normal ranges.

Selection of patients for antiviral therapy

In CHB, transient elastography is likely to be most useful in situations where liver biopsy is recommended and measuring liver stiffness can obviate the need for an invasive procedure. In the current Asia-Pacific consensus statement and the American Association for the Study of Liver Diseases (AASLD) guidelines on the management of CHB, liver biopsy is recommended for patients aged >40 years with ALT <2× upper limit of normal (ULN) and HBV DNA >20,000 IU/mL (for HBeAg-positive patients) or >2,000 IU/mL (for HBeAg-negative patients) [39, 40]. Those patients with significant fibrosis would be candidates for antiviral therapy. It has not been well documented how many patients with ALT levels between 0.5 and 2× ULN have significant fibrosis/cirrhosis. Identification of these patients is important not only for antiviral treatment, but also for the implementation of variceal and HCC screening.

Monitoring response to antiviral therapy

For patients already on antiviral therapy, transient elastography may have a potential role in monitoring disease response to treatment, and to assess the regression of liver fibrosis. Previous studies have demonstrated the reversal of fibrosis in CHB patients receiving long-term antiviral therapy [41, 42]. However, apart from clinical trial settings, the on-treatment assessment of fibrosis using repeated liver biopsies is usually not practicable. In a study of 20 patients who were commenced on entecavir therapy, the median liver stiffness decreased from 11.2 to 7.8 kPa ($p = 0.009$) [43]. In another study of 58 Chinese patients with CHB and elevation of ALT from 1 to 10× ULN, there was a significantly lower median liver stiffness after commencement of antiviral therapy with normalization of ALT compared to pretreatment levels (6.4 vs. 7.9 kPa, respectively, $p < 0.001$). Despite these encouraging results, the use of transient elastography in this setting is confounded by the effect of ALT and inflammation on liver stiffness. The decline in liver stiffness may be due to the decline in inflammatory activity rather than a true improvement in fibrosis, and further studies with paired liver stiffness and histological data are needed to answer this uncertainty. It would be more informative for treatment response to have serial LSMs after normalization of ALT in the course of long-term treatment. Performing repeated measurements at close interval is unlikely to be of benefit, as fibrosis regression is unlikely to be reflected over short periods.

Disease prognosis

As transient elastography is a relatively new technology, studies on the usefulness of LSM in predicting long-term outcomes including HCC and liver-related mortality are limited. In a large prospective study of more than 800 patients with chronic hepatitis C followed up for a mean period of 3 years, liver stiffness was an independent predictor of subsequent development of HCC [44]. Similar results were also demonstrated for patients with CHB. In HBeAg-negative CHB patients followed up for a median length of 35 months, those with liver stiffness ≥10 kPa had a higher cumulative incidence of HCC (9 vs. 0%, respectively, $p < 0.001$) and liver-related mortality (4 vs. 0%, respectively, $p < 0.001$) compared to those who had lower stiffness scores [45]. Another recent study of 1,130 CHB patients showed that in addition to older age, male gender, and heavy alcohol intake, a LSM of >8 kPa was associated with a significant risk of developing HCC [46]. Moreover, there was an increase in hazard ratio with increasing gradient of liver stiffness, from 3.07, 4.68, 5.55, and 6.6 for liver stiffness 8.1–13, 13.1–18, 18.1–23, and > 23 kPa, respectively. The results of these studies demonstrate that transient elastography can be useful as a screening tool to risk stratify CHB patients so that HCC screening and close monitoring can be implemented for those in the high-risk group.

In patients with established cirrhosis, there is evidence that the degree of liver stiffness elevation may be predictive of underlying cirrhotic complications. Correlation between liver stiffness and the presence of esophageal varices has been reported in several studies predominantly involving chronic hepatitis C patients [47–50]. However, not all studies have shown correlation between liver stiffness and variceal size. Furthermore, the cut-off liver stiffness values for the prediction of large (grade $\geq$2) varices in these studies were variable with suboptimal specificity. This may be explained by the fact that variceal size is dependent on the degree of portal hypertension, which is not directly related to the severity of the cirrhosis. The use of transient elastography is currently insufficient to predict the presence or absence of varices in CHB patients with cirrhosis, and upper endoscopy screening is still recommended.

Effects of inflammation on liver stiffness

Now there is unequivocal evidence showing that liver stiffness can be affected by the degree of underlying liver inflammatory activity. One of the earliest evidences suggesting that inflammation can increase liver stiffness values was from a large population study of 1,196 Chinese patients with CHB, showing a positive correlation with ALT levels and LSMs [51]. Subsequent studies showed that severe flares of hepatitis may reduce the accuracy of transient elastography in determining liver fibrosis [52–55]. In a study of patients with severe flares of hepatitis B (defined as ALT > 10× ULN) followed up prospectively for 1 year, there was a significant decline of liver stiffness from the time of severe flare, at 3–6 months, and at 12 months (16.8 vs. 7.9 vs. 6.9 kPa, respectively, all p <0.05) [56]. In fact, a subgroup of patients underwent repeat elastography 4 weeks from the time of flare, and a significant decline in liver stiffness was already evident at that early time point. The liver stiffness score was much higher than the expected value for the stage of fibrosis observed on liver histology. This suggests that the increase in liver stiffness was likely attributed to the inflammatory infiltration rather than actual fibrosis or cirrhosis.

It is likely that even lesser degrees of liver inflammation can affect LSM in patients with CHB. This was suggested by an earlier study showing a gradient of liver stiffness in patients with ALT <0.5× ULN, 0.5–1× ULN, 1–2× ULN, and 2–5× ULN (5.6, 6.5, 8.3, and 10.6 kPa, respectively, all p <0.001) [51]. A recent study of 58 CHB patients with ALT 1–10× ULN who achieved normalization of ALT with a median time of 3 months after commencing oral antiviral therapy showed a significant lower median liver stiffness compared to the baseline measurements (6.4 vs. 7.9 kPa, respectively, $p < 0.001$) [57]. The AUROC curve for diagnosing F2 fibrosis in patients with elevated ALT was 0.68 compared with 0.73 after ALT normalization, suggesting a lower diagnostic accuracy of transient elastography in subjects with elevated ALT levels [57].

Effects of steatosis on liver stiffness

The concurrent existence of metabolic syndrome or hepatic steatosis in CHB patients may increase the risk of fibrosis and cirrhosis. In a study of 1,466 patients with CHB, metabolic syndrome was found to be an independent risk factor for advanced liver fibrosis [58]. Metabolic syndrome and steatosis may also affect liver stiffness. In a study of 429 healthy subjects without known liver disease, liver stiffness was found to be significantly higher in those with metabolic syndrome compared to those without (6.51 vs. 5.33 kPa, respectively, p <0.0001) [21]. It remains a possibility that fat within hepatocytes may alter the propagation time of the shear wave through the liver, thereby affecting the liver stiffness values. The diagnostic accuracy of transient elastography appears to be preserved in Asian subjects with nonalcoholic fatty liver disease [14, 59], although it was shown in a recent study to be reduced in European subjects [60].

Diagnostic models and algorithms

Several models have been developed to further improve the diagnostic accuracy of transient elastography in patients with CHB. To take into the account the effect of elevated ALT as described previously, an algorithm using different liver stiffness cut-off values was derived for normal and elevated ALT levels (defined as > 1–5× ULN) to diagnose bridging fibrosis (> 9.0–12.0 kPa and > 12.0 kPa, respectively) and cirrhosis (>12.0 and >13.4 kPa, respectively) [16]. Based on this model, an estimated 62 and 58% of patients with normal and elevated ALT, respectively, could avoid a liver biopsy.

Other studies have looked at combining transient elastography with another noninvasive modality using biochemical markers to improve the diagnostic accuracy. Combining the use of transient elastography and Forns index (using platelet count, GGT, age, and cholesterol) was shown to improve the specificity of diagnosing advanced fibrosis from 87 to 98% in a validation cohort of 82 CHB patients [61]. In another study of 330 CHB patients, the use of liver stiffness and spleen diameter to platelet ratio index (LSPRI) improved the AUROC for diagnosing cirrhosis from 0.919 for liver stiffness alone to 0.956 when combined with spleen diameter and platelet levels ($p = 0.032$) [62]. The use of less commonly available biomarkers

including serum haptoglobin, apolipoprotein A1, and a2-macroglobulin levels to construct a scoring index (the HALF index) was shown to have a significantly higher AUROC for predicting significant fibrosis compared with transient elastography alone (0.915 vs. 0.877, respectively, $p = 0.01$) [63].

Discordant results

In addition to inflammatory activity within the liver, other factors may cause discordant results between transient elastography and liver biopsy staging of fibrosis. In a study of 251 patients with chronic liver disease from viral hepatitis B and C and nonalcoholic steatohepatitis, discordance between liver fibrosis estimated by transient elastography and biopsy occurred in one out of seven patients. Factors which were associated with discordant results included mild fibrosis (F0–F2), higher BMI, ALT, and interquartile range to median (IQR/M) liver stiffness ratio [64]. In another study of 189 CHB patients, the BMI and lower stages of fibrosis (F0–F2) were identified as independent predictors of significant discordance between histology and liver stiffness [65].

Limitations

Although transient elastography is a rapid and easy procedure, there are some limitations. To ensure the reliability of liver stiffness results, strict adherence to quality criteria should be followed. At least ten valid shots must be obtained; the median value of the valid shots being representative of the final liver stiffness of the patient. In examinations where zero valid measurement is obtained, it is termed a failed scan. The success rate, which is defined as the number of valid shots divided by the total number of shots, should also be $\geq$60%. Finally, the IQR/M ratio should be $\leq$ 30%. In those patients with less than ten valid measurements, or a success rate of <60%, or an IQR/M rate of >30%, the results would be considered as unreliable or suboptimal. In an early study of 2,114 examinations, the failure rate was 4.5%. The only factor associated with failure was a BMI >28 [66]. In a more recent study of 13,369 examinations, the failure rate (as defined by zero valid measurements) was 3.1%, with BMI, operator experience, older age, and type 2 diabetes being independent factors associated with scan failure. Unreliable scans were noted in a further 15.8% of cases using the three criteria as discussed previously, resulting in a total of 18.9% cases with unreliable liver stiffness results [67]. In Asian patients, the other common cause for failed scan includes narrow intercostal spaces (seen mainly in young thin females). In an intention-to-diagnose analysis, the high rate of unreliable results may reduce the accuracy of transient elastography.

Conclusions

Despite the absence of consensus guidelines, LSM using transient elastography has become one of the most widely used methods in the noninvasive assessment of liver fibrosis. It is a rapid procedure with immediate results, and liver stiffness has been shown to significantly correlate with the level of fibrosis in CHB patients. It is a much welcomed alternative to liver biopsy, and studies have shown that an estimated 50–60% of patients with viral hepatitis can avoid a liver biopsy by undergoing transient elastography [16, 68, 69]. Given the absence of adverse effects and the ease of the procedure, there is a potential for population and disease screening for the presence of significant liver fibrosis. In addition to the assessment of liver fibrosis, there is now increasing evidence to show that LSM may have a longitudinal role in assessing disease progression, therapeutic response, and in predicting liver-related complications. Further validation studies are required to confirm the role of transient elastography in these settings.

The increasing use of transient elastography is most likely the consequence of patients and clinicians not wanting or advocating liver biopsies, respectively. However, it should not be viewed as a replacement for other tests of liver fibrosis, as there are important limitations. The major limitations of transient elastography include the reduced diagnostic accuracy with lower fibrosis stages (F0–F2) and in patients with elevated ALT. Therefore, the results should always be interpreted by a qualified clinician according to the clinical context, taking into account the patient demographics and laboratory parameters. Other tests of liver fibrosis, including biomarkers of fibrosis, should be considered as complementary tests to transient elastography, and in situations where liver stiffness is nondiagnostic or inconsistent with the clinical picture, a liver biopsy is still recommended.

Finally, the focus now should include the development of consensus statements on the use of transient elastography in clinical practice, and to incorporate this technology into the current CHB management guidelines. In addition, LSM in assessing fibrosis can be fine-tuned, incorporating known factors such as age, ALT, steatosis, and BMI into diagnostic algorithms so that the accuracy can be further optimized.

References

1. Lai CL, Ratziu V, Yuen MF, et al. Viral hepatitis B. Lancet. 2003;362:2089–2094
2. Lee W. Hepatitis B virus infection. N Engl J Med 1997;337: 1733–1745
3. Pagliaro L, Rinaldi F, Craxi A, et al. Percutaneous blind biopsy versus laparoscopy with guided biopsy in diagnosis of cirrhosis: a prospective, randomized trial. Dig Dis Sci 1983;28:39–43
4. Maharaj B, Maharaj RJ, Leary WP, et al. Sampling variability and its influence on the diagnostic yield of percutaneous needle biopsy of the liver. Lancet 1986;1:523–525
5. Bravo AA, Sheth SG, Chopra S. Liver biopsy. N Engl J Med 2001;344:495–500
6. Lindor KD, Bru C, Jorgensen RA, et al. The role of ultrasonography and automatic-needle biopsy in outpatient percutaneous liver biopsy. Hepatology 1996;23:1079–1083
7. Perrault J, McGill DB, Ott BJ, et al. Liver biopsy: complications in 1,000 inpatients and outpatients. Gastroenterology 1978;74: 103–106
8. 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(7):968–973
9. 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
10. 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;128:343–350
11. de Ledinghen V, Douvin C, Kettaneh A, 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
12. Corpechot C, El Naggar A, Poujol-Robert A, et al. Assessment of biliary fibrosis by transient elastography in patients with PBC and PSC. Hepatology 2006;43:1118–1124
13. Nahon P, Kettaneh A, Tengher-Barna I, et al. Assessment of liver fibrosis using transient elastography in patients with alcoholic liver disease. J Hepatol 2008;49:1062–1068
14. Wong VW, Vergniol J, Wong GL, et al. Diagnosis of fibrosis and cirrhosis using liver stiffness measurement in nonalcoholic fatty liver disease. Hepatology 2010;51:454–462
15. Marcellin P, Ziol M, Bedossa P, et al. Noninvasive assessment of liver fibrosis by stiffness measurement in patients with chronic hepatitis B. Liver Int 2009;29:242–247
16. 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
17. Friedrich-Rust M, Ong MF, Martens S, et al. Performance of transient elastography for the staging of liver fibrosis: a meta-analysis. Gastroenterology 2008;134:960–974
18. Tsochatzis EA, Gurusamy KS, Ntaoula S, et al. Elastography for the diagnosis of severity of fibrosis in chronic liver disease: a meta-analysis of diagnostic accuracy. J Hepatol 2011;54(4): 650–659.
19. Kim DY, Kim SU, Ahn SH, et al. Usefulness of FibroScan for detection of early compensated liver cirrhosis in chronic hepatitis B. Dig Dis Sci 2009;54:1758–1763
20. 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;14:6154–6162
21. Roulot D, Czernichow S, Le Clesiau H, et al. Liver stiffness values in apparently healthy subjects: influence of gender and metabolic syndrome. J Hepatol 2008;48:606–613
22. Sirli R, Sporea I, Tudora A, et al. Transient elastographic evaluation of subjects without known hepatic pathology: does age change the liver stiffness? J Gastrointestin Liver Dis 2009;18:57–60
23. Colombo S, Belloli L, Zaccanelli M, et al. Normal liver stiffness and its determinants in healthy blood donors. Dig Liver Dis 2011;43(3):231–236
24. Kim SU, Choi GH, Han WK, 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
25. Fung J, Lai CL, Chan SC, 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
26. Lai CL, Yuen MF. The natural history and treatment of chronic hepatitis B: a critical evaluation of standard treatment criteria and end points. Ann Intern Med 2007;147:58–61
27. Andreani T, Serfaty L, Mohand D, et al. Chronic hepatitis B virus carriers in the immunotolerant phase of infection: histologic findings and outcome. Clin Gastroenterol Hepatol 2007;5:636–641
28. Kumar M, Sarin SK, Hissar S, et al. Virologic and histologic features of chronic hepatitis B virus-infected asymptomatic patients with persistently normal ALT. Gastroenterology 2008;134:1376–1384
29. Tsang PS, Trinh H, Garcia RT, et al. Significant prevalence of histologic disease in patients with chronic hepatitis B and mildly elevated serum alanine aminotransferase levels. Clin Gastroenterol Hepatol 2008;6:569–574
30. Nguyen MH, Garcia RT, Trinh HN, et al. Histological disease in Asian-Americans with chronic hepatitis B, high hepatitis B virus DNA, and normal alanine aminotransferase levels. Am J Gastroenterol 2009;104:2206–2213
31. Wang CC, Lim LY, Deubner H, et al. Factors predictive of significant hepatic fibrosis in adults with chronic hepatitis B and normal serum ALT. J Clin Gastroenterol 2008;42:820–826
32. Seto WK, Lai CL, Fung J, et al. HBV DNA levels predict significant liver histology for HBeAg-negative chronic hepatitis B patients. Gastroenterology 2010;138:S788
33. Chan HL, Tsang SW, Liew CT, et al. Viral genotype and hepatitis B virus DNA levels are correlated with histological liver damage in HBeAg-negative chronic hepatitis B virus infection. Am J Gastroenterol 2002;97:406–412
34. Zacharakis G, Koskinas J, Kotsiou S, et al. The role of serial measurement of serum HBV DNA levels in patients with chronic HBeAg(-) hepatitis B infection: association with liver disease progression: a prospective cohort study. J Hepatol 2008;49: 884–891
35. Yuen MF, Ng IO, Fan ST, et al. Significance of HBV DNA levels in liver histology of HBeAg and Anti-HBe positive patients with chronic hepatitis B. Am J Gastroenterol 2004;99:2032–2037
36. Cadranel JF, Lahmek P, Causse X, et al. Epidemiology of chronic hepatitis B infection in France: risk factors for significant fibrosis—results of a nationwide survey. Aliment Pharmacol Ther 2007;26:565–576
37. Maimone S, Calvaruso V, Pleguezuelo M, et al. An evaluation of transient elastography in the discrimination of HBeAg-negative disease from inactive hepatitis B carriers. J Viral Hepat 2009;16:769–774
38. 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;33:455–465
39. Liaw YF, Leung N, Kao JH, et al. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2008 update. Hepatol Int 2008;3:263–283
40. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. Hepatology 2009;50:661–662
41. Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, et al. Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B for up to 5 years. Gastroenterology 2006;131: 1743–1751
42. Chang TT, Liaw YF, Wu SS, et al. (2010) Long-term entecavir therapy results in reversal of fibrosis/cirrhosis and continued histologic improvement in chronic hepatitis B patients. Hepatology 2010;52(3):886–893
43. Enomoto M, Mori M, Ogawa T, 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
44. 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;49:1954–1961
45. Fung J, Lai CL, Seto WK, et al. (2010) Prognostic significance of liver stiffness for hepatocellular carcinoma and mortality in HBeAg-negative chronic hepatitis B. J Viral Hepat 2011;18: e200–e205
46. Jung KS, Kim SU, Ahn SH, et al. Risk assessment of hepatitis B virus-related hepatocellular carcinoma development using liver stiffness measurement (FibroScan). Hepatology 2011;53:885–894
47. 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
48. Kazemi F, Kettaneh A, N'Kontchou G, et al. Liver stiffness measurement selects patients with cirrhosis at risk of bearing large oesophageal varices. J Hepatol 2006;45:230–235
49. Vizzutti F, Arena U, Romanelli RG, et al. Liver stiffness measurement predicts severe portal hypertension in patients with HCV-related cirrhosis. Hepatology 2007;45:1290–1297
50. 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;27:1261–1268
51. Fung J, Lai CL, Fong DY, et al. Correlation of liver biochemistry with liver stiffness in chronic hepatitis B and development of a predictive model for liver fibrosis. Liver Int 2008;28:1408–1416
52. Coco B, Oliveri F, Maina AM, et al. Transient elastography: a new surrogate marker of liver fibrosis influenced by major changes of transaminases. J Viral Hepat 2007;14:360–369
53. Arena U, Vizzutti F, Corti G, et al. Acute viral hepatitis increases liver stiffness values measured by transient elastography. Hepatology 2008;47:380–384
54. Sagir A, Erhardt A, Schmitt M, et al. Transient elastography is unreliable for detection of cirrhosis in patients with acute liver damage. Hepatology 2008;47:592–595
55. Wong GL, Wong VW, Choi PC, et al. Increased liver stiffness measurement by transient elastography in severe acute exacerbation of chronic hepatitis B. J Gastroenterol Hepatol 2009;24:1002–1007
56. Fung J, Lai CL, But D, et al. Reduction of liver stiffness following resolution of acute flares of chronic hepatitis B. Hepatol Int 2010;4(4):716–722
57. Fung J, Lai CL, Cheng C, et al. Mild-to-moderate elevation of alanine aminotransferase increases liver stiffness measurement by transient elastography in patients with chronic hepatitis B. Am J Gastroenterol 2011;106 (3):492–496
58. Wong GL, Wong VW, Choi PC, et al. Metabolic syndrome increases the risk of liver cirrhosis in chronic hepatitis B. Gut 2009;58:111–117
59. Yoneda M, Yoneda M, Mawatari H, et al. Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with nonalcoholic fatty liver disease (NAFLD). Dig Liver Dis 2008;40:371–378
60. Gaia S, Carenzi S, Barilli AL, et al. Reliability of transient elastography for the detection of fibrosis in non-alcoholic fatty liver disease and chronic viral hepatitis. J Hepatol 2011;54:64–71
61. Wong GL, Wong VW, Choi PC, et al. Development of a non-invasive algorithm with transient elastography (Fibroscan) and serum test formula for advanced liver fibrosis in chronic hepatitis B. Aliment Pharmacol Ther 2010;31:1095–1103
62. Kim BK, Han KH, Park JY, et al. A novel liver stiffness measurement-based prediction model for cirrhosis in hepatitis B patients. Liver Int 2010;30:1073–1081
63. Lee HJ, Seo YS, Kim DJ, et al. Application of the HALF index obviates the need for liver biopsy in half of all patients with chronic hepatitis B. J Gastroenterol Hepatol 2011;26(6):987–995
64. Myers RP, Crotty P, Pomier-Layrargues G, et al. Prevalence, risk factors and causes of discordance in fibrosis staging by transient elastography and liver biopsy. Liver Int 2010;30:1471–1480
65. Kim SU, Seo YS, Cheong JY, 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
66. Foucher J, Castera L, Bernard PH, 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
67. Castera L, Foucher J, Bernard PH, et al. Pitfalls of liver stiffness measurement: a 5-year prospective study of 13, 369 examinations. Hepatology 2010;51:828–835
68. Pinzani M, Vizzutti F, Arena U, et al. Technology Insight: noninvasive assessment of liver fibrosis by biochemical scores and elastography. Nat Clin Pract Gastroenterol Hepatol 2008;5:95–106
69. Afdhal NH, Curry M. Technology evaluation: a critical step in the clinical utilization of novel diagnostic tests for liver fibrosis. J Hepatol 2007;46:543–545