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

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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 ~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

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 ~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 centrilobular 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 $S \geq 3$ 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
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 \( \leq 30 \) (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 \(<7.2 \text{ kPa} \) [25]. This cut-off value is lower than the cut-off value used for significant fibrosis without an overlap.

**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] |
|------------|-----------------------|---------------------|------------------|-----------------|
| Number     | 173                   | 188                 | 58               | 98              |
| Ethnicity  | French                | Italian             | Chinese          | Korean          |
| F \( \geq 2/S \geq 3 \) | | | | |
| 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           |
| Sensitivity| 93                    | 86                  | 100              | 75             |
| Specificity| 87                    | 96                  | 88               | 93             |
| PPV        | 38                    | 87                  | 75               | 78             |
| NPV        | 99                    | 96                  | 100              | 92             |
| LR (+)     | 7.1                   | 23.1                | 8.6              | 11.1           |
| LR (–)     | 0.08                  | 0.14                | 0                | 0.27           |

**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 >10⁵ 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 ≥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.

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