Clinical Application of Transient Elastography (Fibroscan®) in Liver Diseases

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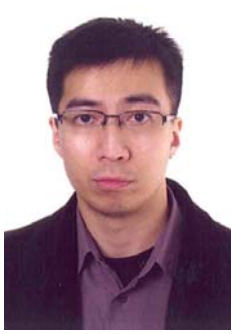

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Introduction

In patients with chronic liver diseases, determination of the severity of liver fibrosis is important for prognostic reasons, and for identifying patients who will benefit from treatment. For those patients already receiving treatment, assessment of liver fibrosis can determine their response to treatment. In addition, hepatocellular carcinoma and variceal screening can also be implemented for patients identified with underlying cirrhosis. At present, liver biopsy remains the current gold standard for assessing liver fibrosis, even though the diagnostic accuracy is limited by the specimen size and fragmentation, sampling error, and inter-observer variability. The accuracy of liver biopsy can be reduced to 80% because of these limitations.[1] Furthermore, liver biopsy is an invasive procedure which can be associated with significant morbidity and rarely mortality, rendering it less acceptable by patients.[2]

In the past few years, however, transient elastography (FibroscanR, Echosens, France) has been increasingly used as a non-invasive tool for the assessment of liver fibrosis by measuring liver stiffness. The probe consists of an ultrasound transducer which is located at the end of a vibrating piston (Figure 1). The piston produces a vibration of low amplitude and frequency, which generates a shear wave that passes through the skin and liver tissue. The ultrasound then detects the propagation of the shear wave through the liver (at a depth from 25 to 65 mm below the skin surface) by measuring its velocity. The shear wave velocity is directly related to the tissue stiffness, with a higher velocity equating to higher tissue stiffness, corresponding to increasing severity of fibrosis. The advantages of transient elastography are that the results are immediately available, and the procedure is painless, rapid (~3 minutes per patient), and easy to perform. The test is performed with the patient lying in the supine position, with the probe placed at the intercostal space overlying the liver (Figure 2). Ten validated measurements are required, with the median value taken as the final result, which is expressed in units of kilopascals (kPa). Transient elastography has been shown to be highly reproducible with minimal inter- and intra-observer variability.[3] The range of possible liver stiffness values obtained with transient elastography is from 2.5 to 75.0 kPa, with the normal liver stiffness value for healthy individuals being around 5.5 kPa.[4] The age of the subject does not affect liver stiffness, and males tend to have a slightly higher liver stiffness value compared to females.[4]

Although transient elastography is an easy and rapid procedure, strict adherence to quality criteria should still be followed to ensure the reliability of the results obtained. The interquartile range of all the readings should not exceed 30% of the final result (the median value), and the success rate of the scans should be greater than 60%. The results should always be interpreted by a qualified clinician according to the clinical context, taking into account the patient demographics, disease aetiology, and laboratory parameters. If the liver stiffness value appears to be discordant with the clinical scenario, then consider repeating a scan or proceed to a liver biopsy.

Figure 1. The probe of the Fibroscan

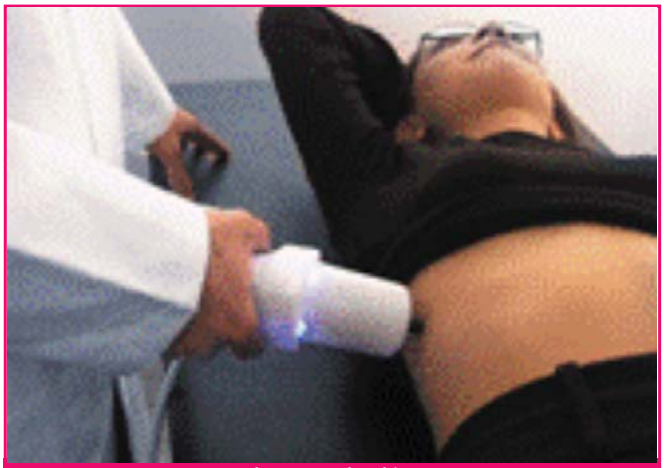

Figure 2. Positioning of patient for fibroscan

Assessment of Fibrosis

The earliest validating studies of transient elastography have been performed on patients with chronic hepatitis C.[5, 6] Many other studies have been performed since

then on other liver diseases including chronic hepatitis B, hepatitis C/human immunodeficiency virus co-infection, non-alcoholic steatohepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, and recurrent hepatitis C after liver transplantation.[7-11] In a meta-analysis of 50 studies assessing the performance of transient elastography, the mean area under receiver operating characteristics curve (AUROC) for the diagnosis of significant fibrosis, severe fibrosis, and cirrhosis were 0.84, 0.89, and 0.94 respectively.[12] The consistent finding of the individual studies was the excellent performance of transient elastography for the diagnosis of severe fibrosis and cirrhosis. For lesser degrees of fibrosis, the performance was more heterogeneous, and dependent on the underlying liver disease.

One of the important aspects of liver stiffness measurements is the cut-off values that are adopted for different stages of fibrosis, with higher cut-off levels corresponding to higher fibrosis stages. The cut-off levels are also different for different diseases. Therefore it is important to interpret the results with the cut-off values specific for the underlying condition. A summary of the cut-off values used for specific liver diseases is shown in Table 1. Because of the variability in cut-off values (even within the same disease), the use of cut-off ranges rather than a single cut-off value should be employed. For example, in patients with liver stiffness <7.0 kPa, there is likely minimal or no fibrosis, whereas cirrhosis is likely in patients with liver stiffness >12.5 kPa (Figure 3).

Table 1.

Aetiology	F2	AUROC	F3	AUROC	F=4	AUROC	Ref
HBV[7]	7.2	0.81	8.1	0.93	11.0	0.93	6
HCV[30]	7.1	0.83	9.5	0.90	12.5	0.95	
HCV[6]	8.8	0.79	9.6	0.91	14.6	0.97	5
HCV/HIV[8]	4.5	0.72	-	-	11.8	0.97	7
PBC or PSC[10]	7.3	0.92	9.8	0.95	17.3	0.96	9
NAFLD[9]	6.6	0.87	9.8	0.90	17.5	0.99	8

HBV=chronic hepatitis B. HCV=chronic hepatitis C. HIV=human immunodeficiency virus. PBC=primary biliary cirrhosis. PSC=primary sclerosing cholangitis. NAFLD=non-alcoholic fatty liver disease. AUROC=area under receiver operating characterstics curve.

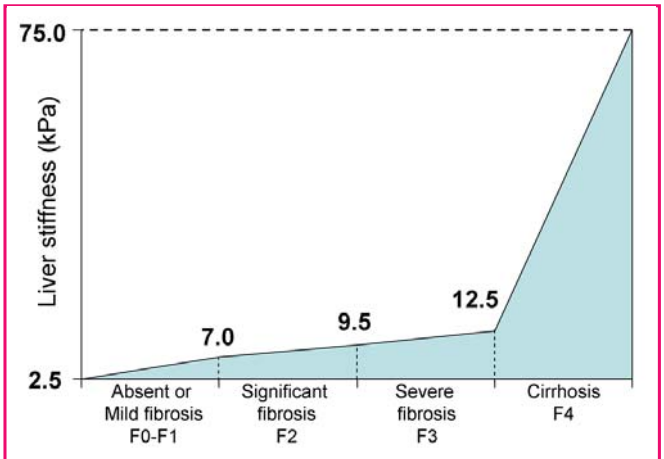

Figure 3. Example of liver stiffness cut-off values and their ranges: correlation with stages of fibrosis

Chronic Hepatitis B

In Hong Kong, chronic hepatitis B constitutes the majority of liver disease seen. One of the main reasons for determining fibrosis in these patients is to identify eligible patients for antiviral therapy. In the current Asian-Pacific guidelines for CHB treatment, liver biopsy is recommended for patients who are over the age of forty with ALT<2x upper limit of normal (ULN) and HBV DNA >20,000 IU/mL (HBeAg-positive) or > 2,000 IU/mL (HBeAg-negative).[13] Those patients with significant fibrosis would be candidates for antiviral therapy. According to the guidelines, these patients would be ideal candidates for transient elastography where a liver biopsy can be avoided. In patients with normal ALT and liver stiffness value <6.0 kPa, no treatment is required, whereas those with liver stiffness values >9.0 kPa should be considered for treatment. In patients with ALT 1-5x ULN, those patients with liver stiffness value <7.5 kPa can be observed, whereas those with value >12.0kPa should be considered for treatment. In patients with liver stiffness values outside these criteria, liver biopsy should be considered.[14] Using this strategy, liver biopsy can be avoided in a significant proportion of patients.

Assessment of Treatment Response

On-treatment assessment of liver fibrosis has been used as a surrogate marker of treatment response and success in patients with chronic liver diseases. In CHB patients, long-term antiviral treatment has been shown to improve histological stages of fibrosis using paired liver biopsies.[15] However, outside clinical trial settings, on-treatment assessment using liver biopsy is usually not feasible. A non-invasive technique such a transient elastography is ideal in this clinical setting. In chronic hepatitis C patients treated with pegylated interferon alpha-2b and ribavirin, liver stiffness values are significantly decreased (compared to pre-treatment values) in those patients with a sustained virological response compared with those that do not achieve sustained virological response.[16] The preliminary study suggests a role of liver stiffness measurement to assess improvements in fibrosis stages of patients on treatment. However, the decline in liver stiffness values may be due to decline in inflammation rather than fibrosis, and further studies with histological follow-ups are required to determine the use of transient elastography in this setting.

Predictive and Prognosis Application

As described above, different cut-off values exist for the different stages of fibrosis. In patients with established cirrhosis, there is evidence that the degree of liver stiffness elevation may be predictive of underlying complications related to cirrhosis. Correlation between liver stiffness values and the presence of oesophageal varices has been reported in several studies.[17-20] However, not all studies have shown correlation between liver stiffness values and variceal size.[18] In addition, the cut-off liver stiffness value for prediction of large (grade 2 or 3) varices in these studies were variable with suboptimal specificity. Without further validation studies, transient elastography is currently insufficient to predict the presence or absence of oesophageal varices in cirrhotic patients, and upper endoscopy is still required for screening.

As transient elastography is a relative new technology, the long-term prognostic application of liver stiffness

measurement is now only becoming available. In a large prospective study of over 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 hepatocellular carcinoma.[21] If these findings are confirmed, then there is potential for transient elastography to be used as a screening tool to stratify patients' risk of hepatocellular carcinoma, and to implement screening and closer monitoring for high risk patients.

Screening

One of the major advantages of non-invasive investigations is their potential use as a screening tool. Using a cut-off of 7.1 kPa, significant fibrosis and cirrhosis can be excluded with a very high negative predictive value (>90%)[22]. This is especially useful in populations where liver disease is prevalent. In a large population study of over 1,300 patients with CHB in Hong Kong, 34% of patients were found to have severe fibrosis. Even in patients with ALT 0.5-1x ULN, 30% had severe fibrosis.[23] Identifying asymptomatic patients with significant fibrosis and cirrhosis through screening will have significant implications on the management of this disease. Other potential populations for screening include those at risk of non-alcoholic fatty liver disease, and those with significant alcohol intake or a history of intravenous drug use. Further studies are required to determine whether transient elastography is useful for population screening in other prevalent liver diseases, such as non-alcoholic fatty liver disease.

Limitations

There is an approximately 5% failure rate associated with transient elastography. The major cause of failed scans is obesity. In Asian patients, other common causes for failed scan include narrow intercostal spaces (seen mainly in young thin females) and adipose tissue overlying the thoracic area. Newer probes to address both obese patients and patients with narrowed intercostal spaces will become more widely available in the near future, and validation studies will be required to determine their diagnostic accuracy. As the pulse is not transmitted well through fluid, transient elastography is not possible in the presence of ascites.

Other factors may affect the liver stiffness value, reducing the diagnostic accuracy. One of the most important factors is with severe flares of hepatitis (ALT >10x ULN), during which the liver stiffness value may be spuriously high, returning to normal levels after resolution of the flares.[24, 25] In our centre, 100% of our CHB patients with severe flares had abnormal liver stiffness, of which 26% had normalised their liver stiffness 3-6 months after their episode of flares.[26] Therefore, transient elastography performed at the time of severe flares will lead to over-diagnosis of severe fibrosis and cirrhosis. Caution should be taken into interpreting elevated liver stiffness results in patients with significant elevation of ALT. There is evidence that lesser degree of ALT elevation in both CHB and chronic hepatitis C can also increase liver stiffness values.[27, 28] The exact mechanism for the increase in liver stiffness seen with liver inflammation remains to be determined.

Whether steatosis increases liver stiffness is debatable. In studies of chronic hepatitis C, steatosis did not appear to affect liver stiffness values.[5, 6] Even in a study of non-alcoholic fatty liver disease, liver stiffness correlated with fibrosis but not steatosis.[9] However, in healthy subjects, the presence of metabolic syndrome is associated with slightly higher levels of liver stiffness.[4] In non-diabetic patients with genotype 1 chronic hepatitis C, insulin resistance also contributed to liver stiffness independent of liver fibrosis.[29] Therefore, the true extent in how steatosis may affect liver stiffness remains unclear.

Conclusions

Over the past few years, significant progress has been made in the use of transient elastography in clinical practice. Despite the absence of consensus guidelines regarding the use of liver stiffness measurements in clinical practice, transient elastography is already widely used in many places, including Hong Kong. This widespread use is probably the consequence of patients and clinicians not wanting or advocating liver biopsies respectively. Transient elastography has been shown to be an excellent diagnostic tool if strict quality criteria are applied, ensuring the reliability of the results. In addition, there is now increasing evidence to suggest that liver stiffness measurements may have a longitudinal role in assessing disease progression, therapeutic response, and in predicting liver-related complications. These roles should be confirmed once long-term outcome data become available. Finally, the main focus now should be on the development of validated guidelines on the use of transient elastography, and to incorporate this new technology into current treatment guidelines.

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