

# IS THERE STILL A PLACE FOR LIVER BIOPSY FOR THE EVALUATION OF CHRONIC LIVER DISEASES IN THE ERA OF NON-INVASIVE METHODS?

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Chronic liver diseases are quite frequent in daily medical activity. Chronic viral hepatitis (B or C), alcoholic or non-alcoholic liver diseases (ASH or NASH) are not rarely encountered and the evaluation of such patients is an important part of a hepatologist' activity. Confronted with such a patient, correct disease assessment is important for the decision of treatment (especially in chronic viral hepatitis) and for prognosis. But what does assessment mean? Usually we want to find out the severity of necro-inflammation (grading) and the stage of fibrosis (staging) in the liver. In some liver diseases, the presence of typical histological signs of disease should be assessed (such as in ASH, in primary biliary cirrhosis - PBC, in autoimmune hepatitis).

For many years **liver biopsy** (most frequently performed percutaneously) was the "gold standard" for evaluation in patients with chronic liver disease. By using echoguided liver biopsy (LB) or blind LB, a hepatic sample is obtained for staging and grading the disease. But this classic assessment modality has some limitation: not always the liver fragment is large enough for a correct evaluation of fibrosis [1], not all the patients accept this invasive procedure and, last but not least, sometimes LB is followed by minor or major complications [1].

More than 10 years ago, the hepatologists started to use non-invasive means for the evaluation of liver diseases. Using **biological tests** such as FibroTest-ActiTest, FibroMax, APRI, Lock, ELF or others, we are able to make a quite correct evaluation of activity (necro-inflammation) and fibrosis in the liver (FibroTest-ActiTest) or of steatosis, NASH and ASH (FibroMax). These types of tests were developed firstly in France and subsequently spread around the world. The cost of such tests exceeds in some cases 100 Euros, but the advantage is that they are totally non-invasive.

Quite at the same time with the biological tests, the first **ultrasound based elastographic method** for fibrosis assessment - **Transient Elastography** (TE - FibroScan®, Echosens, Paris, France) was developed. The principle of this method is that mechanical excitation

of the hepatic tissue induces shear-waves into the liver, whose speed, quantified by ultrasound, is indicative of fibrosis severity. Hundreds of thousands of patients were already evaluated by TE, the accuracy ranging from 80 to 95%. At least 3 meta-analyses [2-4] proved the value of this method for liver fibrosis assessment and showed a strong direct correlation between TE values expressed in kPa and the severity of fibrosis. However this method has some limitations: valid measurement can be obtained only in approximately 85% of subjects [5] or less [6], liver assessment by TE is impossible when ascites is present and TE measurements are irrelevant in patients with high values of aminotransferases, with obstructive jaundice, or with congestive heart failure.

TE has been proven to be accurate firstly in patients with C chronic hepatitis, and subsequently in other pathological conditions, such as chronic B viral infection, NASH, ASH or PBC. Thus, TE was included in the Guidelines of the European Association for the Study of the Liver (EASL), as a standard method for liver fibrosis assessment in HCV patients.

Approximately 5 years ago, another ultrasound based elastographic method appeared on the market - "**point**" **shear wave elastography** (ARFI). By this method, using ultrasound imaging, a precise region is selected in real time into the liver. By pushing a button, an acoustic push pulse is generated by the transducer that induces shear-waves into the liver, whose speed, also quantified by the system, expressed in m/s, is indicative of fibrosis severity. Several studies showed a good correlation between the ARFI values and the severity of fibrosis [7], both in C and B chronic hepatitis [8]. Two meta-analyses [9, 10] showed that the accuracy of this method ranges from 80 to 95% for fibrosis assessment and that the accuracy increases with fibrosis severity. The study of Bota et al [10] also showed that ARFI is non-inferior as compared with TE. Another "point" shear wave elastographic method is **ElastPQ**. Preliminary results showed the same good correlation between the values obtained by ElastPQ and liver fibrosis [11].

In the last three years, a new ultrasound based elastographic method was developed – **2D shear wave elastography** (SWE). It is a color coded method that also displays numeric values. Published papers showed promising results of this method for liver fibrosis assessment [12-14].

Also in the last years, several studies were performed using **strain elastography** (a color coded method), with promising results regarding the evaluation of liver fibrosis severity.

Thus, since so many non-invasive modalities are available, the question that arises is if there still is a place for LB in chronic liver disease patients. In clinical practice, at least in Europe and Romania [15] a dramatic reduction in the number of LB was observed. This reduction is not so important in USA, where TE or ARFI were only recently accepted by FDA.

In Romania there are university centers [15], in which LB was totally abandoned in favor of non-invasive means of evaluation. But in which cases can we renounce to perform LB? In patients with C chronic hepatitis, in which we must treat the infection, regardless of fibrosis severity. If we want to stratify, to prioritize these patients, the elastographic methods (TE, ARFI or SWE) or FibroTest are good enough for this discrimination. In ASH or NASH patients, using biological tests such as FibroMax, or elastographic methods, we can estimate the severity of fibrosis or steatosis (FibroMax). In other diseases, such as B hepatic chronic infection or autoimmune hepatitis, liver biopsy can still be needed. Why? In HBV infection, not only fibrosis severity matters, inflammation also seems to be important, which can be evaluated by ActiTest or by LB. On the other hand, in autoimmune hepatitis, morphological signs such as interface hepatitis are important for diagnosis and prognosis.

On the other hand, some studies have shown that elastographic methods can underestimate the severity of liver disease and can deprive the patient of an adequate therapy. Thus, when significant fibrosis is demonstrated by elastographic methods, therapy can be initiated. In cases with elastographic values smaller than the cut-off proposed for significant fibrosis, maybe a LB should be performed. Some authors [16] propose a combination of biological and elastographic tests to evaluate chronic liver disease patients. In concordant cases, LB can be avoided. For the others, LB is still an option.

Finally, to answer the question from the title, I believe that in the next future the demand for liver biopsy will decrease everywhere, but a number of patients will still need to undergo this procedure for a correct staging of the liver disease. Future developments of ultrasound based elastographic methods (maybe strain elastography or 2D-SWE) or MRI elastography will make liver biopsy obsolete.

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