



Checkmate to liver biopsy in chronic hepatitis C?

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Abstract

Liver biopsy (LB) has traditionally been considered the gold standard for pretreatment evaluation of liver fibrosis in patients with chronic hepatitis C (CHC). However, LB is an invasive procedure with several shortcomings (intra- and interobserver variability of histopathological interpretation, sampling errors, high cost) and the risk of rare but potentially life-threatening complications. In addition, LB is poorly accepted by patients and it is not suitable for repeated evaluation. Furthermore, the prevalence of CHC makes LB unrealistic to be performed in all patients with this disease who are candidates for antiviral therapy. The above-mentioned drawbacks of LB have led to the development of non-invasive methods for the assessment of liver fibrosis. Several noninvasive methods, ranging from serum marker assays to advanced imaging techniques, have proved to be excellent tools for the evaluation of liver fibrosis in patients with CHC, whereas the value of LB as a gold standard for staging fibrosis prior to antiviral therapy has become questionable for clinicians. Despite significant resistance from those in favor of LB, noninvasive methods for pretreatment assessment of liver fibrosis in patients with CHC have become part of routine clinical practice. With protease inhibitors-based

triple therapy already available and substantial improvement in sustained virological response, the time has come to move forward to noninvasiveness, with no risks for the patient and, thus, no need for LB in the assessment of liver fibrosis in the decision making for antiviral therapy in CHC.

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INTRODUCTION

Chronic hepatitis C (CHC) is a major public health concern, with around 180 million individuals affected worldwide^[1]. Liver fibrosis and its end-point cirrhosis are the main causes of morbidity and mortality in patients with CHC^[2]. Information on the stage of liver fibrosis is useful in patients with CHC not only for estimation of prognosis, but also for indication of antiviral therapy. Early international guidelines, consensus statements and expert panel opinions on the management of CHC unanimously recommended that decisions on treatment should be made only after performing a liver biopsy (LB) for pretreatment evaluation of the disease^[3-5]. Consequently, antiviral treatment for patients with CHC has been indicated only for those with moderate to severe

stages of fibrosis (Metavir F2, F3 or F4), while patients with no or minimal fibrosis (Metavir F0, F1) have not been treated^[6]. The rationale of such a strategy was to treat all patients with advanced fibrosis to halt disease progression and prevent complications, rather than those with no or minimal fibrosis who may await better treatments considering the slowly progressing natural history of CHC^[7]. The recommendations mentioned above led to the routine performance of LB in nearly all patients who were newly diagnosed with CHC and potential candidates for antiviral therapy. More recent guidelines^[8] still recommend LB in making treatment decisions, although it has been recognized that it is not necessary in patients with genotype 2 or 3, who can have as high as a 80% sustained virological response (SVR) rate.

For several decades, LB has been widely regarded as the gold standard for the staging of liver fibrosis^[9]. However, LB is an invasive procedure and it is sometimes associated with rare but severe complications^[10]. In addition, LB has several drawbacks (intra- and interobserver variability in histopathological interpretation, sampling errors, variable accessibility, high cost) which raises questions about its value for pretreatment assessment of liver fibrosis in patients with CHC^[11,12]. Nowadays, many clinicians no longer cite LB as the gold standard but, at best, it can only be considered an imperfect standard for the staging of liver fibrosis^[13]. It was this context that, in recent years, triggered a huge interest in the noninvasive assessment of liver fibrosis in patients with CHC. The introduction of a noninvasive methodology for the assessment of liver fibrosis as an alternative to LB in patients with CHC represents a major advancement in clinical hepatology^[14]. Many of the noninvasive methods demonstrated accuracy to a considerable degree in identifying significant fibrosis, particularly cirrhosis, and consequently, noninvasive assessment of fibrosis is already a reality in patients with CHC^[15]. Obviously, with the recent therapeutic development in CHC and reliable noninvasive diagnostic procedures available, LB has lost both its monopoly in the pretreatment assessment of fibrosis and the influence on decision making for antiviral therapy in patients with CHC.

CASE AGAINST LB

For the last 50 years, LB has been considered the gold standard for the staging of liver fibrosis in spite of its several shortcomings: intra- and interobserver variability in histopathological interpretation^[16,17], sampling errors^[18,19], and potentially life-threatening complications^[20,21]. In clinical practice, we frequently encounter the intra- and interobserver variability in the staging of liver fibrosis^[16,17]. Diagnostic errors made by nonspecialist pathologists were reported in > 25% of patients undergoing LB in academic centers^[22,23]. According to a recent study^[24], community pathologists understaged liver fibrosis in > 70% of cases with CHC. Several studies have shown that sampling errors occur when the LB specimen size is too small for an accurate estimation of fibrosis^[18,19]. Both the

length and the diameter of the biopsy core may affect the accuracy of fibrosis stage evaluation in patients with CHC^[25,26]. Obviously, the shorter and thinner the samples are, the greater is the number of misclassifications of liver fibrosis. There is some controversy among pathologists in defining an adequate LB sample for an accurate staging of liver fibrosis. Some investigators^[27] suggest that a sample of at least 15 mm in length and containing more than five portal tracts is adequate, while others recommend biopsy samples of 20 mm containing at least 11 portal tracts^[26] or even larger samples, up to 25 mm^[18]. Bigger is better^[28], but at the price of an increased risk of severe complications^[10,18]. However, it should be noted that, in clinical practice, few LB specimens reach an adequate length of 20 mm^[29]. Furthermore, LB only samples an extremely small part of the whole organ (1/50 000) and therefore, there is a risk in the evaluation of lesions that are heterogeneously distributed throughout the entire liver^[21]. LB may underestimate the amount of fibrosis, and cirrhosis could be missed in 10%-30% of cases^[30]. Studies concerning fibrosis staging have also shown differences in one third of cases with CHC between LB samples obtained from the right and left lobes of the liver during laparoscopy^[19]. Data on LB complications are heterogenous and contain wide variations in reported rate from one study to another^[10,20,21,31-34]. Major complications include bleeding and bile peritonitis, with a reported mortality rate ranging from 0.03% to 0.1%^[10,20,31,32,34]. It is worthwhile mentioning that both the transjugular route and ultrasound guidance approaches to LB do not significantly reduce the rate of major complications^[35,36]. Complication rates are higher when LB is performed by less-experienced physicians^[31,37]. In addition, LB is costly, variably available, poorly accepted by patients, and not suitable for repeated evaluation. The cost of an LB in the United States, United Kingdom and Australia varies between 1000 and 2000 USD, and it could go over 3000 USD if complications occur^[12,38-40]. LB is not welcomed by patients and it may be refused by more than half of those with CHC^[41]. LB is inappropriate for a dynamic evaluation of liver fibrosis over time, and recommendation to repeat biopsy every 3-5 years to follow up disease progression is certainly unrealistic, mainly due to patient nonadherence^[40]. LB is contraindicated in the presence of coagulopathy and thrombocytopenia. Last but not least, the prevalence of CHC makes LB impossible in all patients with CHC who are candidates for antiviral therapy. It is these drawbacks of LB that have led to the development of noninvasive methods for the assessment of liver fibrosis in patients with CHC and, hopefully, to a major change in hepatology practice.

Nevertheless, LB has some well-recognized advantages for assessing fibrosis in CHC, such as direct measuring of liver fibrosis, well-established staging system, and evaluation of associated lesions (steatosis, iron deposition, inflammation, alcoholic liver disease, nonalcoholic fatty liver disease, metabolic syndrome), although these diagnostic advantages are counterbalanced by the aforementioned disadvantages.

CASE IN FAVOR OF NONINVASIVE METHODS

Noninvasive methods for detecting liver fibrosis may be divided in two main groups: serum markers of fibrosis and transient elastography (Fibroscan).

Serum markers for liver fibrosis are commonly divided into direct serum markers, which are directly linked to the modifications in extracellular matrix turnover produced by hepatic stellate cells during the process of fibrogenesis in the liver, and indirect serum markers which reflect alterations of the hepatic functions. The direct markers include glycoproteins (hyaluronate, laminin, YKL-40), collagen family (procollagen III, type IV collagen), collagenases and their inhibitors (matrix metalloproteinases, tissue inhibitory metalloproteinase-1), and they are not routinely available in most clinical laboratories. The indirect markers are biochemical parameters determined in routine blood tests [platelet count, prothrombin time, aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio]. Serum markers for liver fibrosis may be used singly^[42-45] or combining panels of direct or indirect serum markers and demographic parameters^[46-55], with the aim of increasing the accuracy of single parameters. Some of them are patent-protected and commercially available: FibroTest[®] (Biopredictive, Paris, France) licensed under the name of Fibrosure[®] in the United States (LabCorp, Burlington, NC, United States)^[51], Fibrometer[®] (BioLiveScale, Angers, France)^[52], Hepascore (PathWest, University of Western Australia, Australia)^[53], ELF[®] (Enhanced Liver Fibrosis Test, iQur Ltd, Southampton, United Kingdom)^[54], and FibroSpect II[®] (Prometheus Laboratory Inc. San Diego, Ca, United States)^[55]. Among these, Fibrotest [α -2-macroglobulin, γ -glutamyl transpeptidase (GT), apolipoprotein A1, haptoglobin, total bilirubin, age, sex] is the most widely used and was validated by several studies on patients with CHC^[56-63]. The reported accuracy of Fibrotest for significant fibrosis/cirrhosis expressed as area under receiving operating characteristic curve (AUROC) ranges from 0.74% to 0.87%^[46,51]. To improve the performance of Fibrotest, its combination with Fibroscan has been suggested; with such a combination, one study reported AUROC of 0.88 for at least F2 (stage in the Metavir scoring system) and 0.95 for F3 or F4^[56]. The sensitivity and specificity of serum-marker-based tests could also be improved by combining them using sequential algorithms. Thus, Sebastiani *et al.*^[64] combined AST/platelets ratio (APRI) with Fibrotest - a combination known as sequential algorithm for fibrosis evaluation biopsy - and found it to have an accuracy of 92.5% in the detection of fibrosis in CHC, obviating 81.5% of liver biopsies. APRI has a slightly lower performance than Fibrotest, with an accuracy between 60% and 82% for significant fibrosis and 60% and 88% for cirrhosis^[46,64], but it is a simple cost-free readily available test in all hospital settings. Both Fibrometer (platelet count, hyaluronate, AST, α -2-macroglobulin, international normalized ratio, urea, age) and Hepascore (bilirubin, γ GT, α -2-macroglobulin, hyaluronic acid, age, sex) showed good

performance for detection of significant fibrosis^[52,53,65].

There are several advantages of serum markers such as high applicability, with no risk for the patient and no contraindication; they can be performed and repeated in outpatient clinics; widespread availability; and inter-laboratory reproducibility^[66]. However, there are some limitations of serum markers: none is liver specific; results are unreliable in comorbidities (hemolysis, Gilbert syndrome, rheumatoid arthritis); and they have poor performance in the diagnosis of intermediate stages of liver fibrosis^[66]. Nevertheless, it is important to note that the performance of each noninvasive marker is evaluated against LB which is an imperfect gold standard, and the apparent failure of noninvasive markers to make an accurate distinction between different stages of intermediate fibrosis could be the consequence of misclassifications from biopsy^[67,68].

Transient elastography (Fibroscan[®], Echosens, Paris, France) measures liver stiffness in a volume at least 100 times greater than a standard LB sample, and therefore, may be more representative of the entire liver. Fibroscan is composed of an ultrasound transducer probe mounted on the axis of a vibrator; vibration is transmitted to induce an elastic shear wave that propagates through the liver. Pulse-echo ultrasound acquisition is used to measure the velocity of the shear wave, which is directly related to liver stiffness: the stiffer the liver, the faster the shear wave propagates. Results are expressed in kPa, and values range from 2.5 kPa to 75 kPa, with normal values < 5.5 kPa^[69]. According to several studies, a cutoff value of 7.2-8.7 kPa defines significant fibrosis, and cirrhosis is diagnosed by a cutoff value of 12.5-14.5 kPa^[70,71]. Fibroscan seems to be a reliable method for the diagnosis of significant fibrosis (AUROC 0.84) and cirrhosis (AUROC 0.95)^[72,73]. Its combination with serum-based tests (Fibrotest, Fibrometer) increases the performance (but also the costs) for the diagnosis of significant fibrosis^[56,71,72]. Among noninvasive methods for diagnosis of cirrhosis, Fibroscan has the highest level of performance^[62,72,73], and its combination with serum markers does not increase accuracy^[63,72].

Fibroscan has several advantages: it is painless; quick (< 5 min); highly reproducible, with results immediately available; inexpensive; and easy to perform in the outpatient clinic and at the bedside^[66]. In addition, Fibroscan can be repeated for longitudinal disease monitoring, which is difficult, if not impossible, with LB. In cirrhotic patients, Fibroscan values correlate with portal pressure (based on the hepatic venous pressure gradient measurement), which is a reliable predictor of clinical outcomes^[74-77], disease severity^[78], and the risk of hepatocellular carcinoma^[79]. Finally, Fibroscan and serum markers are well accepted by patients, therefore, they could be used as screening methods for the detection of liver fibrosis/cirrhosis in at-risk groups^[80] and even in general population^[81], while LB is unacceptable for screening purposes. Fibroscan measurement failure and unreliable results are due to limited operator experience^[82], narrowed intercostal spaces^[82], and obesity^[82,83], although

this last problem seems to be overcome by a new specially designed probe^[84-86]. Results are influenced by ALT flares^[87,88], extrahepatic cholestasis^[89,90], and congestive heart failure^[91].

DISCUSSION

In the past, expert consensus guidelines on the management of CHC unanimously recommended routine LB before initiation of antiviral therapy^[3-5,92,93]. Based on LB findings, treatment has often been advocated only for patients with at least moderate to severe stages of fibrosis (Metavir F2, F3 or F4), and withheld for those with no or minimal fibrosis (F0, F1)^[6,93]. As a consequence, tens of thousands of patients were most likely denied proper antiviral therapy. More recent guidelines^[8,94] recommend LB only in patients with CHC genotype 1 (SVR rate < 50%) in treatment decision making, and consider it unnecessary in those with genotype 2 or 3 who may have an SVR rate as high as 80%. The primary endpoint of antiviral therapy for CHC is achieving SVR - defined as undetectable serum HCV RNA at 24 wk after discontinuation of therapy. Viral eradication prevents disease progression, improves survival, and reduces health care costs associated with the management of complications. Thus, if viral clearance is the aim of antiviral therapy in CHC, then to what degree does an exact histopathological fibrosis stage established through biopsy still matter? With the new protease inhibitor (PI)-based triple therapy (addition of telaprevir or boceprevir to pegylated interferon and ribavirin) available and SVR rates approaching 75% in patients with CHC genotype 1^[95,96], it is clear that LB has lost its importance in the recommendation of antiviral therapy.

During the past 10 years, an intensive debate has taken place between those in favor of LB and those who promote noninvasive methods for pretreatment assessment of liver fibrosis in patients with CHC. There is extensive literature showing the pros and cons of LB or noninvasive methods. As in chess, winning does not come easy for a supporter of noninvasive methods against a supporter of LB with a firmly rooted preference. Step by step, those in favor of non-invasive methods have gained ground, waiting for the final move: checkmate! Today, several noninvasive methods, ranging from serum marker assays to advanced imaging techniques, have proved to be excellent tools for the evaluation of liver fibrosis in patients with CHC. According to the latest European Association of the Study of the Liver clinical practice guidelines^[97] and United Kingdom consensus guidelines^[98] recommendations, noninvasive methods can be used instead of LB in patients with CHC to assess liver disease severity prior to antiviral therapy. It is therefore surprising that many experts in the field of hepatology and the most recent American Association for the Study of Liver Diseases 2011 practice guidelines^[99] favor LB before therapy initiation, despite substantial improvement in treatment success rate for genotype 1 patients with PI-based triple therapy. The

main reason against noninvasive methods for evaluation of liver fibrosis is their apparent failure to make an accurate distinction between different stages of intermediate fibrosis. It is important to note that the performance of each noninvasive method was evaluated in all studies by calculating the AUROC using LB as a reference standard. As LB is an imperfect standard, a perfect noninvasive method will never reach the maximum value (1.0)^[100], and therefore, noninvasive methods are as inaccurate as LB for the assessment of fibrosis stage. Thus, the failure of noninvasive methods to discriminate between different stages of intermediate fibrosis could be the consequence of classification errors from histopathological findings of biopsy^[67,68]. For clinicians, it is more important to know if their patients have no/mild or advanced fibrosis/cirrhosis, rather than the exact pathological scoring system through LB, and this could be easily achieved by means of noninvasive methods. Taking into account that all recent international guidelines^[97-99] recommend treatment with PI-based triple therapy in all patients with CHC genotype 1, provided that they have no contraindications to peg-interferon and ribavirin, the need to stage liver fibrosis accurately is decreasing in treatment decisions.

The final move - checkmate to LB - is, therefore, possible once the rate of SVR has reached 75% with PI-based triple therapy for patients with CHC genotype 1. Consequently, it is clear that in the era of PI-based triple therapy and other new potent direct-acting agents in the pipeline, the information obtainable from LB has little, if any, influence on treatment decisions. It should be underlined that in this article, checkmate to LB in patients with CHC refers strictly to cases with no need for this invasive and risky procedure in therapeutic decision making. With PI-based triple therapy already available in many countries, and an allocation system probably based mainly on medical need (therapy for those likely to develop complications in the next few years), noninvasive methods with the highest accuracy for detecting severe fibrosis/cirrhosis used as an alternative to LB for pretreatment assessment of liver fibrosis in patients with CHC are now part of routine clinical practice. Fibroscan or any patented biomarkers (Fibrotest, Fibrometer and Hepascore) have recently been recommended for first-line staging of liver fibrosis^[101] before deciding on antiviral therapy. However, the adoption rates of noninvasive methods by hepatologists differ from country to country. In France, a survey of 546 hepatologists revealed that 81% of them used noninvasive methods^[102], while in the United States, despite the aforementioned shortcomings of LB, there is still significant resistance to accepting noninvasive methods as an alternative to biopsy. We believe that sooner or later this will change, and the requirement of LB prior to starting antiviral therapy in patients with CHC will be reassessed.

In conclusion, in the era of PI-based triple therapy and other new potent direct-acting agents on the horizon that can achieve SVR rates approaching 100%, the time has come to move forward to risk-free noninvasive

methods for the patient, leaving LB behind in the evaluation of liver fibrosis in decision making for CHC antiviral therapy. In other words, checkmate to LB?

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