Liver fibrosis: Screening is not staging

To the Editor:
The letter by Poynard and colleagues deserves several comments. Like Mehta et al., we agree that when taking liver biopsy as a reference, any non-invasive test should not reach a higher AUROC than the liver biopsy itself, mainly due to the fact that misclassification can occur in staging fibrosis with biopsy [1,2]. The highest AUROC that can be reached is however unclear and clearly dependent on (1) the rate of misclassification in staging with biopsy (2) the conditional relationship between non-invasive markers and liver histology (3) the internal performance of the marker. Interestingly, a recent meta-analysis of Fibroscan showed AUROC of 0.94 for diagnosis of cirrhosis and 0.89 for severe fibrosis taking biopsy as a reference [3]. These very high AUROC values are certainly not related to a lack of power (more than 10,000 patients were pooled) or faking as suggested by Poynard et al. It simply demonstrates that liver biopsy is an acceptable gold standard and that some, but not all non-invasive tools, can compete well with liver biopsy where the diagnosis of cirrhosis or advanced fibrosis is concerned.

In contrast to Poynard et al. we do not believe that a spectrum bias due to different prevalence of stages in different populations can explain the decrease in the AUR-OC when changing the definition of diseased liver or for distinguishing between two adjacent fibrosis stages. In fact, any comparison of surrogate markers restricted to two stages eliminated this spectrum bias! [4]. The explanation for the low performance of markers for distinguishing between two adjacent stages is lack of accuracy, which leads us to reinforce our claim that surrogate markers cannot be used for adequate monitoring of individual fibrosis staging.

Poynard et al. suggest that validation of non-invasive test of fibrosis and comparison with histological staging with biopsy should rely on clinical endpoints. This is of course ideal and surely adequate for any test that evaluates fibrosis independently of histology. Such is the case for imaging techniques or assessment of liver stiffness. This remark is less relevant when considering serum markers of fibrosis. The choice of blood tests included in the marker’s formulas and their respective weights in the algorithm are defined through the prism of histologic assessment of fibrosis with liver biopsy. In this situation, liver biopsy is by definition the gold standard of the serum markers and any weakness of the biopsy will

References

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directly decrease the fitness of the algorithm of the serum marker. Because of this conditional relationship, serum marker performance should at best approach accuracy of liver biopsy. Therefore, it is rather surprising to support serum markers, arguing on biopsy weakness when this tool is chosen to define the formula of serum markers. Finally, Poynard et al. suggest that screening for advanced fibrosis is a public health challenge and this can only be achieved through a moratorium of liver biopsy as a first-line estimate. Anybody would agree that screening of advanced fibrosis does not rely on liver biopsy and that non-invasive tests have excellent accuracy in this setting but there is a major difference between screening for advanced fibrosis and staging fibrosis. Non-invasive tests have shown deceptively low performance in this matter with significant overlap between adjacent stages.

The risk of performing a liver biopsy should always be discussed with regards to the potential benefit for the patient and in this context any dogmatic statement, either in favour or against it, is dangerous. Today, antiviral therapy has still limited efficacy and is associated with serious adverse effects. Therefore management of patients using only a screening procedure for advanced fibrosis, such as serum markers, will clearly lead to an obvious loss of opportunities for patients to be adequately and timely treated, a risk that surpasses the adverse events of the biopsy.

Therefore, in the present situation, non-invasive serum markers are efficient screening instruments for advanced fibrosis or cirrhosis but remain a dead end when addressing the accurate evaluation of liver damage.

References