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Editorial

Is liver biopsy still the gold standard for diagnosing liver fibrosis?

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Assessment of liver fibrosis has gained significant importance for a multitude of liver diseases in recent years. The reasons for this are many. First, a large wealth of information can be elucidated by measuring the extent of liver fibrosis. In many liver diseases, the degree of liver fibrosis has been shown to correlate with the risk of disease progression and outcome. For instance the presence of liver fibrosis is an important indicator of disease progression and poor outcome in non alcoholic fatty liver disease (NAFLD). In a recent natural history study, presence of stage 4 fibrosis was found to be an independent predictor of liver related mortality in patients with non-alcoholic steatohepatitis (NASH).[1] For this reason, patients who are detected with advanced degrees of fibrosis are candidates for early institution of aggressive therapy. This is particularly true for hepatitis C, where for example, in genotype-1 infected individuals even with small SVR rates, therapy should be instituted as soon as possible, if advanced fibrosis is detected. On the other hand, individuals with no or early fibrosis can indeed wait, till the time more effective therapy becomes available.[2]

Another important detail which can be gleaned from repeat assessment of liver fibrosis is the dynamic nature of the liver reparative process. There is now sufficient evidence that with cessation of liver injury, liver fibrosis (even to the extent of cirrhosis) may regress. A large multicentre study on HCV related chronic liver disease (collated data from four separate multicentre randomized controlled trials), showed a reversal of cirrhosis in 75 patients (49% of 153 who had cirrhosis on baseline liver biopsy).[3] In yet another study it was noted that of the 11 patients with hepatitis B and cirrhosis, treated with long term lamivudine, 8 showed significant improvement in their cirrhosis.[4]

The third and most important reason for an emerging interest in liver fibrosis assessment is the development of a number of tools which can detect the degree of liver fibrosis with reasonable accuracy, without resorting to a liver biopsy. This makes assessment of liver fibrosis easier and more reproducible without any risks involved. But whether these tools will render liver biopsy obsolete is yet to be seen.

The strongest criticism against liver biopsy arises over the sampling errors inherent with the procedure. This is because liver biopsies only samples 1/50,000th of the liver volume. It has been shown that the degree of error in fibrosis staging based on one liver biopsy can range from 28 to 50% across various situations.[5-6] The variability has been reported to be higher among patients with non alcoholic fatty liver disease because of heterogeneous distribution of lesions in the liver.[7]The liver pathology in diseases like hepatitis B, C and autoimmune hepatitis are distributed more homogenously and are therefore less likely to be associated with sampling errors. In addition, liver biopsy histopathology is also subject to inter-observer variations in reporting. Lastly, liver biopsy is an invasive procedure associated with a small yet definite risk of morbidity and mortality. The emerging non-invasive technologies circumvent most of the aforementioned drawbacks of liver biopsy.

The non-invasive tools for liver fibrosis assessment are of two types: serum biomarkers and physical methods (elastography). Use of serum biomarkers involves only drawing of blood samples and hence their ease of use. The most frequently used and validated of all such markers is the patented 'Fibrotest' which assesses five variables including: serum bilirubin, haptoglobin, gamma glutamyltranspeptidase, á2-macroglobulin and apolipoprotein A. It has been found to have good discriminative power for detecting higher stages of fibrosis in various forms of liver diseases such as hepatitis C, B, alcoholic liver disease and NAFLD, with an AUROC of ≥0.85.[8] The problem with such biomarker panels is the non-availability of all such markers in standardized assays across different laboratories. Further, the performance of these biomarkers in intermediate stages of fibrosis is still questionable. Aspartate aminotransferase to platelet ratio index (APRI) is another simple non-invasive method for assessing the degree of fibrosis. This test is based on the observation that advancing fibrosis decreases the platelet count due to progressive portal hypertension and is associated with a rise in AST levels over ALT. Many studies have demonstrated good efficacy of this marker in defining liver fibrosis stages.[9,10]

The prototype of physical methods is the 'transient elastography' (TE), or 'Fibroscan' which measures the velocity of a shear wave as it travels through the liver. The velocity is proportional to the stiffness of the liver which in turn is proportional to the degree of fibrosis. Other techniques employing the same principle include ARFI,[11] which has been shown to be effective in detecting advanced fibrosis and MR elastography, which still needs to be validated. TE has been validated against liver biopsies from a number of liver diseases and has demonstrated good accuracy for detecting extremes of fibrosis.[12,13] Again, the performance falls short when it comes to diagnosing intermediate stages of fibrosis.

Studies evaluating the efficacy of non-invasive liver fibrosis assessment tools in pediatric population are limited. Nobili et al, studied the performance of fibroscan in 52 pediatric patients with NASH and demonstrated that it was a good tool for identifying patients at the extremes of the liver fibrosis spectrum (no fibrosis or significant fibrosis). Like in adults the intermediate and adjacent stages are difficult to discriminate.[14]

Sayed et al, in the present issue of the journal, have presented the results of APRI and compared them to liver biopsy findings in 76 children and 37 adults infected with hepatitis C in Cairo, Egypt. They concluded that APRI performed poorly at discriminating advanced fibrosis in the population studied. The AUROC of APRI was only 0.49 for predicting significant fibrosis in pediatric population and 0.63 for predicting significant fibrosis among the adult population. Earlier studies have demonstrated excellent AUROCs for APRI, for predicting significant fibrosis. Wai et al, demonstrated in 78 adult CHC patients an AUROC of 0.88 for detecting significant fibrosis.[10] In a recent meta-analysis including more than 40 studies with 8739 patients, APRI showed an AUROC of 0.77, 0.80 and 0.83 for predicting significant fibrosis, sever fibrosis and cirrhosis respectively.[15]

In the present study, there were no patients with advanced fibrosis in the pediatric group and there were no patients with minimal fibrosis in the adult group. In the pediatric cohort, no patient had F3 or F4 fibrosis and only 22 (29%) had F2 fibrosis. In the adult cohort, no patient had F0 or F1 fibrosis. In essence APRI was used to discriminate between F0 vs. F1-2 fibrosis among children and F2 vs. F3-4 fibrosis among adults. Performance of most non-invasive techniques has been shown to be poor when two adjacent stages have to be discriminated. This lack of the entire spectrum of fibrosis stages in the population studied is one of the major factors for the poor performance of APRI in this study.

McGoogan et al, also studied APRI in 36 subjects between 0-20 years of age, suffering from hepatitis B or C and demonstrated only a moderate performance of this index in detecting fibrosis(AUROC:0.71) or cirrhosis(AUROC:0.52).[16] They also found that the performance was better in children who were older than 13 years of age, signifying the limitation of this tool in very young subjects.

Since this index depends so heavily on the AST values, the variable AST in the study population could also have affected the performance of APRI. In the pediatric population, both the AST and ALT were raised 2-4 times the upper limit of normal, probably as a result of significant hepatic necro-inflammation. The high AST in the pediatric population would have resulted in wrongly predicting advanced fibrosis, when the higher AST values were infact because of active necro-inflammation. Further, the upper limit of normal for both the pediatric population and adult population was taken as 49 IU/l, when it is known that children normally have lower AST level cut-offs.

There has been a lack of studies evaluating the non-invasive tools for liver fibrosis assessment in the pediatric population and this study is an important attempt in this direction. However, because of the above mentioned issues, it has been unable to correctly demonstrate the efficacy of APRI as an effective tool in the pediatric HCV infected population.[17]

Larger studies involving the entire spectrum of liver fibrosis stages in children are needed to validate the non-invasive liver fibrosis assessment tools in pediatric age group. Although the conclusion drawn by the authors is correct that APRI cannot replace liver biopsy as the gold standard, particularly in the pediatric population, it still remains a cheap and effective tool for predicting advanced fibrosis, if employed properly in the right group of patient while keeping in mind its inherent caveats. As has been noted with other non-invasive tools, APRI can also be reliably used to identify patients with extremes of liver fibrosis. But for discriminating intermediate stages, the non-invasive tools cannot replace liver biopsy as the gold standard. So liver biopsy will remain the gold standard for purpose of discriminating all the stages of liver fibrosis, till the time a more robust modality or another standard (such as clinical outcomes) is developed against which we can compare the non-invasive tools.

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