Letters to the Editor

Reply to: The use of acoustic radiation force-based shear stiffness in non-alcoholic fatty liver disease

To the Editor:
We appreciate the comments and clinical perspectives raised by Dr. Cross in response to our recent publication concerning the use of acoustic radiation force-based shear stiffness values in NAFLD patients to evaluate fibrosis scores [1], and we would like to take this opportunity to respond to those points. Dr. Cross mentions the significant number of failed stiffness reconstructions in our study (21.5%), which we agree would be too high for a screening test to evaluate liver fibrosis. It should be noted that the majority of those reconstruction failures (∼84%) occurred in patients with BMI >30. As discussed in the manuscript [1], higher BMI is associated with deeper layers, reduced acoustic radiation force magnitudes, and therefore noisier data for performing the reconstructions. Many of these patients with failed shear wave reconstructions did not meet our quality control threshold of having an IQR/mean ratio of 0.3 over the replicate shear wave estimates in the three imaging locations. This reconstruction variability is an active research efforts focused on improving the next generation of shear wave reconstruction algorithms. Additionally, we would recommend restricting the imaging locations utilized in patients with high BMI to help improve the repeatability of the reconstructed stiffnesses. While the intercostal imaging windows tended to yield repeatable shear wave reconstructions, the addition of the subcostal window was associated with additional variability in this subset of patients, most likely due to the additional subcutaneous fat at this location.

Although an intention-to-treat analysis was not performed in the context of our study, one can argue that knowledge of the absence of advanced NAFLD (i.e. fibrosis stage 3–4) using a non-invasive test would decrease resource utilization and cost associated with performing liver biopsies in all patients with suspected NAFLD. As highlighted in Fig. 2 of the referenced manuscript [1], the shear modulus across the early stages (fibrosis stage 0–2) of disease is very narrow, and those patients do not have increased morbidity or mortality from liver and cardiovascular related outcomes. With the exception of optimizing risk factors for disease progression, patients with early stage disease do not require surveillance and monitoring for complications associated with advanced hepatic fibrosis. We agree with Dr. Cross that additional statistical analyses are necessary to better define the sensitivity, specificity, negative and positive predictive values as well as positive and negative likelihood ratios for such a non-invasive test to have widespread clinical applicability. However, such analyses would ideally include a much larger sample size. Therefore, larger studies powered to derive meaningful threshold values capable of guiding clinical decisions are necessary.

Conflict of interest

The underlying research reported in the study was funded by the National Institutes of Health.

Reference


Transplanted hepatocytes: Wiped out or washed out?

To the Editor:

Hope for the long-term effectiveness of hepatocyte transplantation (HTx) for metabolic liver disease in pediatric patients is based on the premise that hepatocytes in the main constitute a static population, quite unlike for example, the small bowel where there is constant turnover. However, several recent studies on the dynamics of hepatocyte turnover raise important questions about the long-term success of HTx. For example, a recent lineage tracing study in the mouse has demonstrated that, within a year, almost the total parenchymal population is replaced by new hepatocytes differentiating from Sox9-expressing interlobular bile ducts [1,2], suggesting that transplanted hepatocytes will inevitably be ‘washed out’ of the liver within the turnover time – in about 1 year in the mouse. Other murine studies have pointed to a small sub-population of biliary duct cells, also being Sox9-positive, as being bipotential, driving progenitor cell-mediated liver regeneration [3], seemingly giving rise to Foxl1-expressing progenitor cells, also with bipotentiality, but with limited proliferation potential [4]. A further murine study has shown that 0.076% of all albumin-expressing hepatocytes are born from albumin-naïve cells every 4 days in normal healthy mice, again highlighting the dynamic cell state of the normal liver [5].

These murine studies have re-awakened the discussion as to whether hepatocytes ‘stream’ from portal tracts to hepatic veins, first described for the rat liver [6]; subsequently with the liver being formally proposed as a ‘stem cell and lineage system’, hierarchically organized into stem, amplifying and differentiating...