MR Elastography of Hepatic Fibrosis: Elastogram Analysis Strategies

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Introduction MR Elastography[1] (MRE) is a promising method of quantifying liver fibrosis[2-5] that relies on motion sensitised gradients detecting within liver tissue synchronised mechanical wave motion generated by an external driver applied to the body wall overlying the liver. Typical wave frequencies of 30-80Hz are used which represent a compromise between tissue attenuation and spatial resolution. Owing to variation of liver and body anatomy it is difficult to ensure even wave generation across the whole liver. Current methods of analysis use an inversion algorithm[6] to detect wave motion and convert this into a stiffness map or elastogram. Most studies utilise manual ROIs delineating the liver margins on the magnitude image mapped onto a matching elastogram to derive mean liver stiffness values which are correlated with histopathological gradings or collagen stain analysis. There are potential problems with these approaches. Histopathological analysis is limited to a small volume of liver and prone to sampling errors and the grading schemes, even if semi-quantitative tissue stain based, are relatively subjective. There are potential limitations with the MRE analysis as not all of the liver may have quantifiable wave motion present and the inversion algorithm is likely to perform less well at boundaries with rapid changes in tissue stiffness (e.g. liver margins). Several studies report MRE technical failures in hemochromatosis patients where hepatic iron loading shortens T2* reducing SNR for the MRE technique making wave motion undetectable. Small amounts of tissue iron accumulate in other types of chronic liver disease and this might also influence the MRE method in these patients. The primary aim of this work was to compare different analysis ROI strategies using a cohort of previously studied patients who underwent same day MRE and liver biopsy. A secondary aim investigates if T2* is predictive of liver stiffness and if T2* may have a role as a quality metric for MRE liver stiffness measurements.

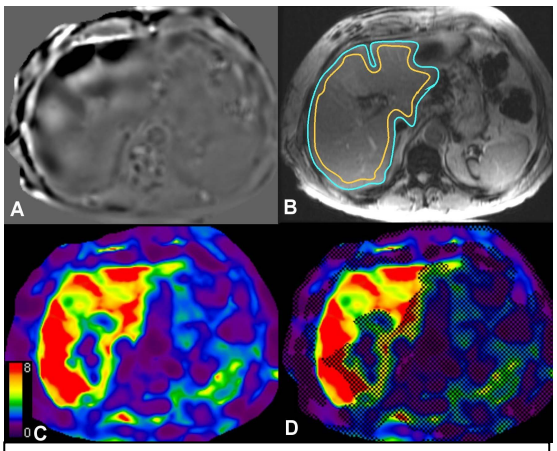

Fig 1. An MRE study of a cirrhotic patient [A] wave image, [B] Outer margin (OM) and sub margin (SM) ROIs, [C] matching colour scaled elastogram (kPa), and [D] wave confidence image mask using a 95% limit

Methods The data from a previous ethically approved study[5] of 71 patients with chronic liver disease and suspected liver fibrosis was re-analysed. MRE examinations were performed with a 1.5T whole body MR system (HDx, GEHT, Waukesha, WI) and a 60 Hz pneumatic driver placed over the ribs superficial to the liver. Using a previously described phase contrast gradient echo sequence[4] and inversion algorithm[6], elastograms were generated at two transaxial levels through the liver. Histopathological analysis used established fibrosis grading schema adapted for underlying aetiology and semi-automated analysis of a Sirius red (SR) stain to derive the percentage of stained collagen in a concatenated section of whole liver biopsy core. These results were normalised by log transformation for subsequent correlation. MRE images were analysed using an ROI delineating the outer liver margin (OM) on the magnitude image and matched to the corresponding elastogram by two independent observers. This was repeated with a sub-marginal (SM) ROI approximately 1cm internal to the liver margin. A wave detection based program (MQ, Mayo Clinic) was applied to the MRE data and a value obtained reflecting measurements only where wave motion was reliably detected in the liver using three different confidence thresholds (MQ93, MQ95, MQ97). Finally the liver T2* was calculated using a multi-echo gradient echo sequence acquired as part of the original study. *Primary analysis* used Pearson's correlations and 95% confidence intervals comparing Sirius Red analysis against respective MRE ROI strategies (OM, SM, MQ93, MQ95 & MQ97). *Secondary analysis* used univariate statistics (Pearson's correlation) to report relationships between T2*, Sirius Red and MRE liver stiffness. MQ95 was used as the standard for MRE liver stiffness. A subsequent multivariate linear regression analysis was performed to assess if T2* remained independently predictive of MRE (MQ95) after accounting for the proportion of liver fibrosis as determined by SR.

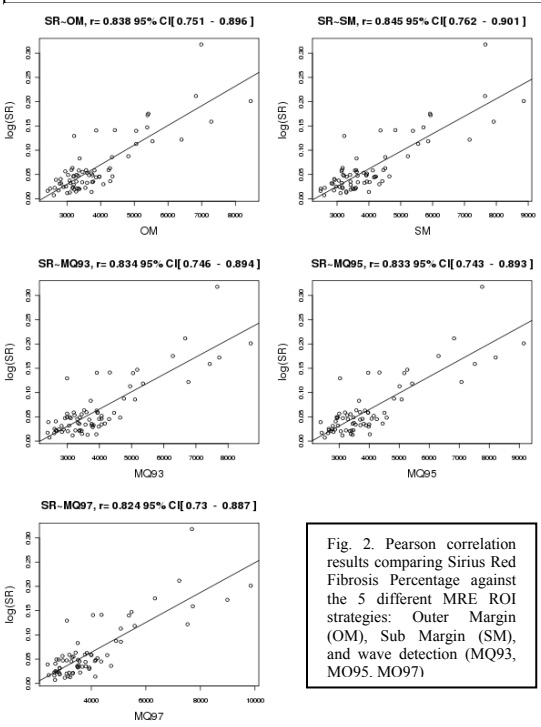

Fig. 2. Pearson correlation results comparing Sirius Red Fibrosis Percentage against the 5 different MRE ROI strategies: Outer Margin (OM), Sub Margin (SM), and wave detection (MQ93, MQ95, MQ97)

Results The primary analysis is shown in Figure 2, indicating that ROI strategy makes no discernible difference in the observed relationship between SR and MRE with all correlations ranging from r = 0.824 to 0.845 with overlapping 95% CIs. This suggests changes in the spatial extent of each ROI and related changes to MRE stiffness distribution makes little difference when summarizing stiffness using summary metrics such as the mean. The secondary univariate analyses assessing the relationships between MRE, T2* and SR observed the following significant relationships (r = 0.362, p=0.002 between MQ95 and T2*, and r = 0.357, p=0.002 between SR and T2*). Multivariate regression analysis testing if T2* and SR are predictive of MRE stiffness (MQ95~T2*+SR) resulted in observed p-values of 0.321 and <0.001 for T2* and SR respectively.

Discussion Counter intuitively the more sophisticated MRE elastogram analysis strategies did not improve correlation of MRE and histopathology results when compared with simple outer margin ROIs. In this study mean stiffness within the defined ROIs was utilised, however other ROI parameters such as the median and the maximum stiffness values may be more appropriate values to compare and future work will investigate this. Although this study observed a statistically significant relationship between T2* and MRE, it does not seem appropriate to consider T2* as a surrogate variable when interpreting the relationship between MRE stiffness and underlying fibrosis, as T2* no longer remains predictive of MRE in a multivariate sense i.e. when factoring in liver fibrosis (as determined by SR).

Conclusion These results indicate that although the specific image quality based analysis criteria in this study can be successfully applied to MRE analysis they do not improve the correlation with histopathology. This may in part be due to the inherent limitations of using histopathological grading schema as a reference standard for MR elastographic measurements of liver stiffness and by correlating with only the mean ROI stiffness values.

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