Liver T_1 increases with fibrosis and is correlated with liver stiffness and ELF score

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TARGET AUDIENCE The ability to stratify cirrhosis (scarring) of the liver is important for clinicians and patients to assess disease severity and ascertain prognosis. The current reference tests to assess cirrhosis are either inadequate for stratification (liver biopsy) or invasive (hepatic venous pressure gradient). The ability to assess cirrhosis using a continuous and non-invasive diagnostic tool, which provides detail of the entire liver, is attractive to healthcare professionals, patients and industry.

BACKGROUND Liver disease is now the 5th largest cause of death in the UK, with a recent study reporting a 68% increase in the prevalence of liver cirrhosis between 1992 and 2001. The gold standard for evaluating the severity of liver disease is a biopsy. However, this procedure is invasive, affected by inter- and intra-observer variations and sampling errors. In the context of significant liver scarring (cirrhosis), liver biopsy provides limited stratification as there can be a spectrum of severity across one categorical stage of disease (e.g. stage 4 in the Metavir classification). The stratification of cirrhosis is imperative for decisions on prognosis and assessing novel compounds in therapies. Two alternative non-invasive methods to stratify cirrhosis use physical or biological approaches. FibroScan® is a recent, physical method to measure liver stiffness [1]; a mechanical pulse is applied, and ultrasound used to measure the resulting wave velocity from which stiffness can be measured and related to fibrosis severity, with a prior study showing a correlation with histopathology [2]. The enhanced liver fibrosis (ELF) test is a biological technique using an algorithm based on serum markers to generate an ELF score [3]. Recently, it has been reported that the MR longitudinal relaxation time (T_1) is elevated in the liver of patients with cirrhosis compared with healthy volunteers [4], using a saturation recovery technique in a single axial slice through the liver. We have recently developed a respiratory-triggered inversion recovery method for multi-slice measures of T_1 in the abdomen, without the need for complicated motion correction methods [5].

AIM To compare the MR longitudinal T_1 relaxation time parameter in the liver with the non-invasive techniques of ELF and Fibroscan® to stratify liver cirrhosis.

METHODS The study was approved by the NHS ethics committee, and all volunteers gave informed, written consent. Patients were studied from a prospective, longitudinal study of compensated cirrhosis (CC) (Child Pugh A). 29 CC patients (18M/11F, age 59 ± 1 yrs (mean±SEM), aetiology: 9 ALD/ 8 HCV/ 6 NAFLD/ 2 Haemochrom./ 1 PBC/ 1 PSC/ 1 HBV/ 1 Autoimmune, MELD score: -0.04 - 10.79). In addition 19 healthy volunteers (HV) were recruited: 12M/7F, age 57 ± 2 yrs. Patients attended on a single day following an overnight fast for a blood test (to evaluate ELF score), FibroScan® and MRI scan. The HV group had only the blood test and MRI scan. FibroScan® measurements were repeated 10 times and a median calculated. MRI was performed using a 1.5T Philips Achieva scanner (body transmit coil, 16-channel SENSE torso receive coil). A modified respiratory-triggered inversion recovery sequence [5] (FOV 288x288 mm, 3x3x8 mm voxel, 3 sagittal slices through liver with 5 mm gap) was used with a spin echo (SE) readout (TE = 27 ms, minimum TR = 5000 ms, FA 90º, SENSE 2). IR-data were acquired at 13 inversion times (*TI)* (100 - 1200 in 100 ms steps, and 1500 ms), with each *TI* being collected at the same point in the respiratory cycle (1500 ms following the respiratory trigger) by introducing an additional delay *Tv* following the trigger and prior to *TI* [5] (first slice acquired at *TI*, subsequent slices spaced 65 ms apart). Data were fit on a voxel-by-voxel basis to a 2 parameter model to generate T_1 and M_0 maps using a least squares non-linear curve fit in Matlab®. A binary mask of the liver, excluding major vessels, was used to obtain a mean T_1 value across the 3 slices of the liver. T_1 values were plotted against stiffness as measured from Fibroscan® and ELF score, and the Pearson correlation coefficient (R) calculated using SPSS 18.

RESULTS AND DISCUSSION The stiffness and ELF score were highly correlated (Figure 1, R=0.71, p=0.001).

*Stiffness***:** (N=27 CC) Figure 2 shows the correlation of T_1 against stiffness measured using FibroScan. The Pearson correlation coefficient between T_1 and stiffness was highly significant, R= 0.725 (p<0.0001).

*ELF score***:** (N=18CC/19HV) The mean liver T_1 was 783 ± 31 ms for CC patients and 645 ± 8 ms for the HV group (p<0.00001) whilst the mean ELF score was 10.8 ± 0.3 for CC and 8.3 ± 0.1 for HV (p<0.00001). Figure 3 shows the correlation of T_1 with the ELF score. For all subjects, there is a highly significant Pearson correlation coefficient of R=0.723 (p<0.0001). A clear distinction is seen between CC and HV, with a mean R=0.617 for CC (p=0.006) and no significant correlation for HV. Figure 4 shows T_1 maps from a single HV and example CC patients with the histogram of T_1, mean T_1, ELF score and stiffness. Heterogeneity of T_1 across the liver is clearly seen, as indicated by the increased FWHM with disease severity, a factor which cannot be assessed using either ELF or Fibroscan® measurements.

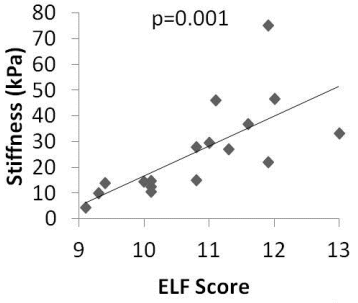

Fig 1: Stiffness measured from FibroScan® v ELF score.

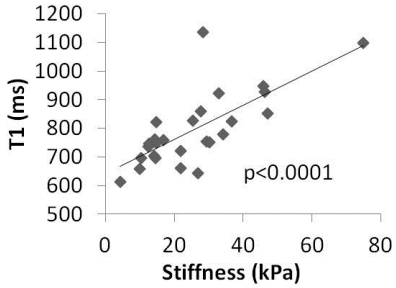

Fig 2: T_1 v stiffness measured using FibroScan®.

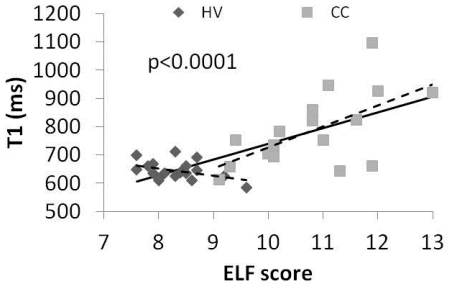

Fig 3: T_1 v ELF score. Solid trendline and p-value shown for all subjects, dashed trendlines for HV and CC groups.

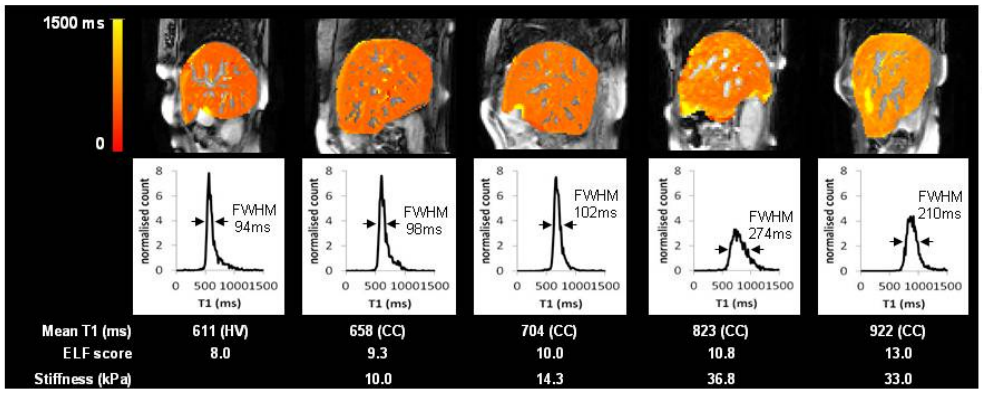

Fig 4: T_1 maps from a single HV and 4 CC patients with mean T_1, normalised T_1 histograms, with corresponding ELF score and stiffness.

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