Multivariate analysis of MRI datasets of the liver: enhancing definition of disease severity by combination of parameters

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INTRODUCTION

Clinically, liver fibrosis occurs as a result of chronic viral exposure (HCV,HBV) and metabolic/lifestyle factors (Non-alcoholic steatohepatitis, alcoholic liver disease). Non-invasive definition of fibrosis and associated components of the pathophysiology would represent a significant advantage in disease diagnosis and development of novel therapies. Diagnosis is currently reliant upon the liver biopsy, the limitations of which are well recognised and include morbidity, mortality and acquisition/interpretation variability [1]. Irrespective of the etiology, the pathophysiology is complex with multiple consequences for the liver. This includes altered composition (steatosis, extracellular matrix) and hemodynamic alteration. Whilst MR methods have been developed for quantifying some of these parameters their utility across the spectrum of disease remains poorly characterised. For soluble liver fibrosis biomarkers, multiple marker measurements are frequently combined, in part defining the limitations of relying upon a single measure for a complex disease process. For imaging applications, could the same approach be of value? Here a multivariate analysis of MR data was performed to assess the utility of combining independent MR parameters for defining disease. MR data acquired and used in this analysis includes magnetisation transfer (MT) to quantify macromolecular composition, fat-water-ratio measurements to quantify steatosis and dynamic contrast enhanced MRI to define hemodynamic factors. The imaging data used was acquired from a CCl_4-induced rat model of liver fibrosis.

METHODS

Model: The animal research protocol was approved by Yale University Institutional Care and Use Committee. 52 male Wistar rats were studied with 14 rats representing a normal control group. The remaining were administered CCl_4 intraperitoneally (three times per week). Different stages of fibrosis were achieved by varying the duration of administration of CCl_4 from 2-16weeks. After imaging, the livers were removed and underwent analysis by a histopathologist using standard methods to define the degree of fibrosis on a scale of 0-5 where 0=normal, 1-3=fibrotic and 4-5=cirrhotic.

MRI acquisition and analysis: MR was performed on a 1.5T Siemens scanner using a wrist coil. MT data was acquired using an FSE sequence with varying offset frequency pairs (±800, ±1600, ±2400, ±3200, ±4000 and ±4800 Hz). For lipid analysis the 3-point Dixon method was applied using TrueFISP (TR = 7.7 ms, TEs = 2.69/3.85/5.01 ms, FOV = 140 x 96, matrix size = 176 x 256, number of averages (NA) = 4, flip angle (α) = 55°, slice thickness 4.5 mm). For dynamic gadolinium scanning a gradient echo sequence (TR/TE = 15/2.1 ms, FOV = 180 x 120, matrix size = 119 x 192, NA = 1, α = 40°, 1 slice (3 mm thick) was used to acquire images before (15s baseline) and after administration of Gd-DTPA (0.05mM/kg). Images were collected with a temporal resolution of 1.3s for 4minutes 30seconds.

Image analysis: MT ratios (MTRs) were defined using signal intensity with (S) and without (So) saturation: $MTR = 100 \times (S_o - S)/S_o$. Fat-water-ratios (FWR) were obtained from the calculated water-only and fat-only images. The dynamic MR data was analysed using a two-input kinetic model, calculating distribution volume (DV), mean transit time (MTT), portal blood flow (PBF), arterial blood flow (ABF) and portal fraction (PF).

Statistical analysis: Multivariate analysis was performed on all rat data where all three imaging techniques had resulted in analysable images (40/52). Initially all variables were included in the analysis. Data were split randomly into training (n=26) and test (n=14) sets. PLS Discriminant Analysis (PLS-DA) was performed which aimed to construct new components (from linear combinations of the original variables) that maximise separation between classes and to define which variables contribute most in providing separation.

RESULTS

Figure 1. shows a PLS-DA plot formed using all variables with a training set showing the distribution of normals, fibrotics and cirrhotics. A test set (n=14) was then applied to the model to assess how predictive it was. A total of 9/14 = 64% were correctly classified. A further optimisation step involved assessing the parameters that contribute most to the discrimination between groups and removing the least significant parameters from the model. Figure 2 shows the relative discriminatory potential of all parameters studied here. The higher the VIP (variable influence on projection) value on the y-axis the greater the contribution to the model. It is assumed that parameters with values less than 1 do not contribute significantly to the model. An optimised model was then produced by focusing on FWR, PF, MTT and DV. A PLS-DA model produced with the reduced parameter set resulted in an improved predictability when the test set was applied (11/14=79%).

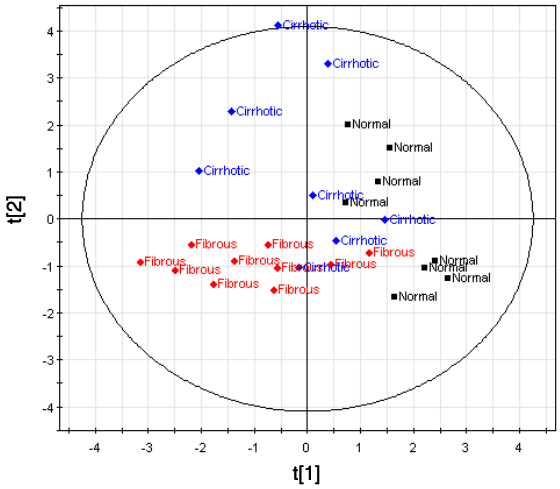

Figure 1. PLS-DA plot from the training set. All MR parameters were included in this analysis.

DISCUSSION

To our knowledge this is the first attempt at formally using a multivariate approach to assess and combine liver MR imaging parameters in the study of hepatic fibrosis. When imaging a complex pathophysiology with multiple derived parameters this multivariate approach offers a rapid method to assess the contribution of individual parameters. In this instance it has helped define which techniques should be considered further and which offer little insight into the disease. When the most promising imaging parameters have been identified the technique can be used to combine parameters and build a representative disease model. In addition to cross-sectional application in a study like this, such a multivariate analysis could be used to sensitively define treatment response by assessing multiple parameters in concert.

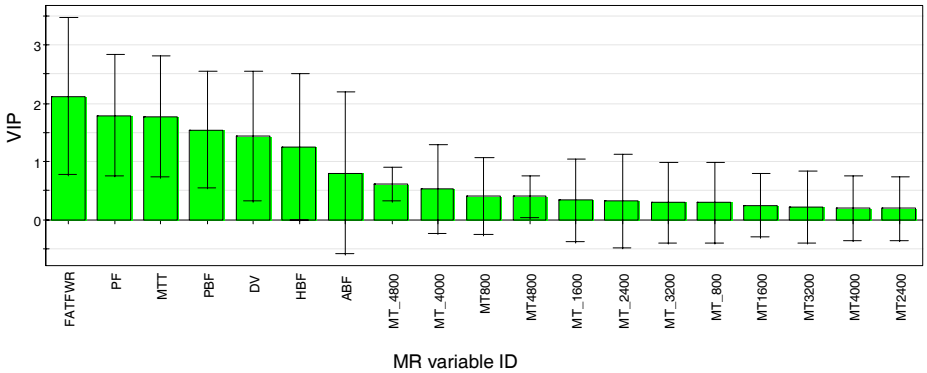

Figure 2. A plot derived from the PLS-DA analysis defining the relative contributions made from all parameters to success of the model. [VIP = variable influence on projection]

REFERENCES

[1] Bedossa et al., *Hepatology* 38(6), 1449, 2003.