# Texture analysis of combined contrast enhanced MR imaging permits accurate non-invasive staging of liver fibrosis

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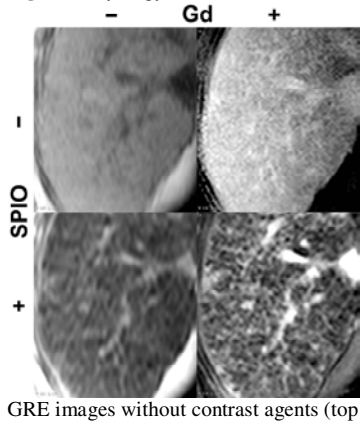
## BACKGROUND

A fundamental alteration in many chronic liver diseases is progressive deposition of collagen in the extracellular matrix (fibrosis). Untreated, fibrosis may progress to cirrhosis and hepatocellular carcinoma. Early diagnosis is important to initiate treatment and halt disease progression. The current diagnostic gold standard is liver biopsy, which stages the severity of liver fibrosis on a five-point ordinal scale ranging from F0 (normal) to F4 (cirrhosis) (1). However, biopsy has several drawbacks. Only 1/50,000$^{th}$ of the liver is sampled, which leads to sampling errors and limits the utility of biopsy for longitudinal assessment. Biopsy is associated with a 1-3% risk of complication requiring hospitalization and 1/10,000 risk of death (2). Thus, there is a need to develop non-invasive imaging methods to safely diagnose, grade, and monitor fibrosis.

A promising magnetic resonance (MR) method to grade liver fibrosis is combined contrast enhanced (CCE) imaging. **CCE imaging** directly visualizes fibrosis by using two synergistic contrast agents, superparamagnetic iron oxides (SPIOs) and a low molecular weight gadolinium (Gd) chelate. **SPIOs** accumulate in Kuppfer cells within normal liver and regenerative nodules and cause signal loss on gradient recalled echo (GRE) images. Fibrotic tissue lacks Kupffer cells, does not accumulate SPIOs, and does not lose signal. **Gd chelates** distribute freely into the extracellular space during equilibrium phase and preferentially accumulate in and cause signal enhancement of tissues with relatively large interstitial compartments, such as fibrosis. Thus, SPIOs and Gd both improve the visibility of fibrosis by different mechanisms. Individually, each agent is of limited efficacy but, in combination, the two agents depict liver fibrosis with high clarity as a meshwork of high-signal reticulations superimposed on low-signal liver tissue (**Figure 1**).

Quantitative texture analysis has been used on unenhanced MR imaging to non-invasively classify liver in a binary fashion as normal (F0) or cirrhotic (F4) (3,4). Texture analysis is a way to quantify complex visual patterns within an image using simpler sub-patterns that have characteristic texture features. Because CCE imaging shows fibrosis with greater clarity than unenhanced imaging, we **hypothesized** that texture analysis of CCE MR imaging would permit non-invasive staging (F0-F4) of fibrosis. The **purpose** of this study was to assess non-invasive staging of fibrosis using texture analysis of CCE MR imaging with histology as the reference.

**Figure 1.** Synergy of SPIOs and Gd




GRE images without contrast agents (top L), with SPIOs (bottom L), with Gd (top R), with both SPIOs and Gd (bottom R)

## METHOD AND MATERIALS

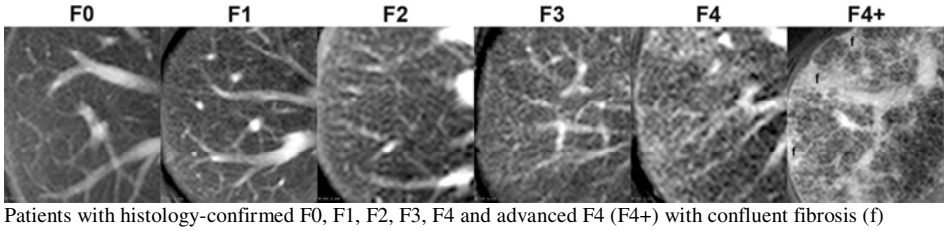
122 adults with various stages of **histology-confirmed** fibrosis (20 F0, 12 F1, 10 F2, 10 F3, 70 F4) were imaged at 1.5T after combined administration of SPIOs and Gd. Breath-held GRE acquisitions were obtained (8 mm slice thickness, no gaps, TR 80-140 msec, TE 4.6 msec, matrix 256x256, 30-40 cm FOV, flip angle 70°). A radiologist, blinded to patient identity and pathology results, scored the GRE images qualitatively on a 5-point ordinal scale designed to match the 5-point histology scale. The radiologist also measured subjects' abdominal anterior-posterior dimension (skin to skin) and transferred three representative images offline. Texture analysis on the three images was performed using MaZda software (v 3.2 [3,4]) on operator-selected regions of interest. For each region, 256 quantitative texture features were computed. Features were averaged within patients and correlation analyses were performed to reduce the number of features. A forward selection algorithm based on a Bayesian information criterion was used to build a model to predict histological fibrosis stage from the remaining features. Fitted values from the final model were used to generate a single quantitative MR fibrosis score for each patient. The qualitative MR score, quantitative MR score, and histology fibrosis stage were compared pairwise (Pearson correlation). Sensitivity and specificity for diagnosis of severe fibrosis or cirrhosis (F≥3) were calculated for both MR scores.

## RESULTS

CCE MR images showed fibrosis as high-signal reticulations. Reticulations were thicker, denser, and more clearly visible in patients with more advanced fibrosis (**Figure 2**). The final quantitative MR model had nine texture features. Of these features, two were based on first order histogram data, which quantifies the spread of the pixel intensity histogram. Three were based on second order histogram data, which are functions of the joint probability of pixel pairs along all directions at different distances in the image. Four were based on discrete wavelet transforms.

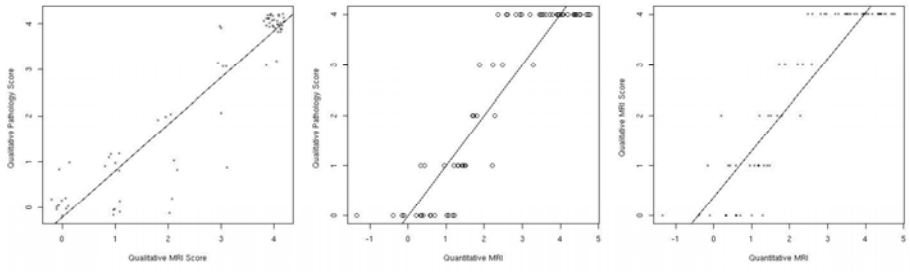
Pairwise Spearman correlation analysis showed excellent agreement between qualitative MR and pathology (rho = 0.911), quantitative MR and pathology (rho = 0.929), and qualitative MR and quantitative MR (rho = 0.908) (P<0.0001 for all) (**Figure 3**). For diagnosis of F≥3, both the qualitative and the quantitative scores had sensitivity of 1.00 (38/38)[95% confidence intervals, 0.91-1.0] and specificity of 0.94 (29/31)[0.79-0.99]. Results were identical after stratification by abdominal anterior-posterior dimension.

**Figure 2**. CCE gradient echoes in patients with different stages of histology-confirmed fibrosis




Patients with histology-confirmed F0, F1, F2, F3, F4 and advanced F4 (F4+) with confluent fibrosis (f)

**Figure 3.** Scatter plots of qualitative MR and pathology, quantitative MR and pathology, and qualitative MR and quantitative MR




## CONCLUSIONS

To our knowledge, the imaging-histology correlation shown here is higher than any reported in the literature using other imaging techniques. Moreover, results were identical in patients stratified by abdominal size, suggesting the technique is likely to succeed in obese subjects. Future work will assess the effect on texture analysis of motion and other artifacts, image noise, image contrast weighting, spatial resolution and other imaging parameters, and contrast agent dose.

**References**:

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