An Approach to Graphically Evaluate Steatosis in Non-Alcoholic Fatty Liver Disease

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Introduction Hepatic steatosis affects 30% of the adult population in the western world [1] and is characteristic of many chronic liver diseases. Currently, the gold-standard to determine the severity of liver disease, including steatosis, is liver biopsy, which is an invasive procedure prone to sampling error due to small specimen size (less than 1/50,000th of the liver) [2]. A major pitfall in the assessment of steatosis is its heterogeneous distribution. While MRI provides a non-invasive alternative to liver biopsy for quantification of steatosis with opposed-phase T1-weighted GRE imaging [3], the method depends on manually drawn regions of interest and cumbersome mathematical equations. Furthermore, quantification is affected by placement of regions of interest and could be misleading in the assessment of disease progression. The aim of this study was to develop a color mapping technique based on liver signal intensity loss on in- and out-of-phase images to readily and accurately assess the steatosis grade and heterogeneity.

Methods 38 patients diagnosed with non-alcoholic fatty liver disease (NAFLD, 20 men and 18 women; mean age 44 years, range 11-73) and 20 healthy volunteers (10 men and 10 women; mean age 31 years, range 22-48) underwent MRI using a 1.5T GE scanner. Coronal breath-hold T1-weighted dual fast gradient echo sequences were acquired of the abdomen (TR/TE 90/4.2 and 2.1 ms; flip angle 75°; slice/gap 8/1 mm; matrix 256x128-192, NEX 1). Patients underwent a liver biopsy for steatosis grading within 3 months of the MRI scan (average 23.7 days, median 12 days, range 0-83 days). The number of subjects with steatosis grades 0, 1, 2 and 3 were 5, 7, 11 and 15, respectively.

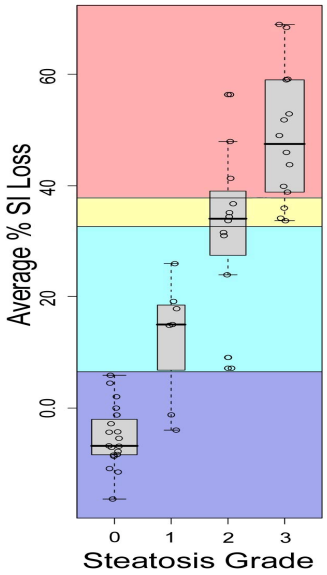


Figure 1. Used recursive partitioning to find cut-off points of % SI Loss to signify steatosis grades 0-3.

First, we compared average signal intensity (SI) values and histopathological steatosis grades to find cut-off points of the SI values that differentiated steatosis grades 0, 1, 2, and 3 (Figure 1). In order to determine liver SI loss for each subject, 12 1.5 – 2 cm^2 regions of interest (ROIs) were measured to create the average liver SI and 3 ROIs were measured for the average spleen SI on anatomically matched in- and out-of-phase images. Liver SI loss was calculated using a previously described formula (Eq1) [4]. We used recursive partitioning to establish the optimal cut-off points of liver SI loss for steatosis grades (0 - 3).

$$SILoss = \left(\frac{SI_{in,liver}}{SI_{in,spleen}} - \frac{SI_{out,liver}}{SI_{out,spleen}}\right) / \left(\frac{SI_{in,liver}}{SI_{in,spleen}}\right)$$

Equation 1. Used to find SI Loss from the dual phased images

Second, the cut-off points were used to threshold SI loss images and color was used to facilitate liver steatosis assessment. In order to generate the color maps of liver steatosis, we used a semi- automated program to calculate the percent SI difference on a pixel by pixel basis on all slices of the liver to create a new 3D set of images representing liver SI loss. We used our calculated cut-off points with 4% margins for error to threshold the pixels with color, such that dark blue, aqua, green, yellow, orange, and red signified steatosis grades 0, 1, borderline 1-2, 2, borderline 2-3, and 3, respectively (Figure 2). Borderline colors were included to represent transitional areas where subjects could be classified either way.

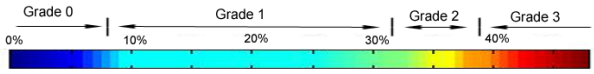
The liver was manually segmented from the color mapped image and overlaid on the in-phase T1 coronal image (Figure 3, 4). These color maps were visually assessed for steatosis severity and heterogeneity by two trained researchers and their responses were compared to each other as well as to histopathological results. Steatosis grade was defined as the average of the predominant grades (Figure 3). Heterogeneity (Figure 4) was defined by less than 90% predominance of any color in the liver.

Results SI loss increased with steatosis grade, yielding cut-off points (Table 1) where 43/58 cases were correctly classified. Using the color maps, the two readers correctly predicted the biopsy steatosis grade in 42/58 (κ =0.59) and 45/58 (κ = 0.67), while 12/16 and 9/13 of the incorrectly graded livers were considered heterogeneous, respectively. They both found heterogeneous steatosis in 60.5% of the NAFLD patients and 10% of the healthy volunteers with excellent interobserver agreement (κ = 1.0). Overall, the readers agreed well on steatosis grading (κ = 0.89, 95% CI 0.80- 0.99).

% SI loss cut-off points	Steatosis grade
<7	0
7-31	1
32-37	2
≥38	3

Table 1 - %SI Loss Cut-off points for Steatosis Grades.

Figure 2. Index used for coloring SI loss images.



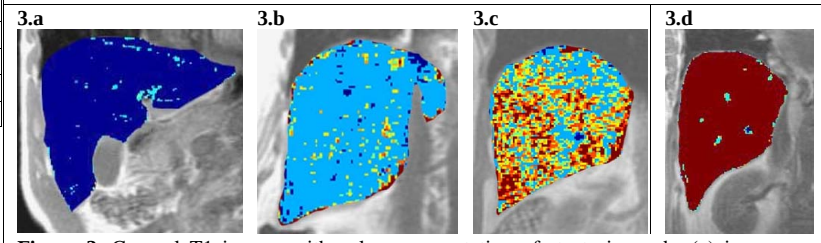


Figure 3. Coronal T1 images with color representation of steatosis grade. (a) is an example of steatosis grade 0, (b) is steatosis grade 1, (c) is steatosis grade 2, and (d) is steatosis grade 3.

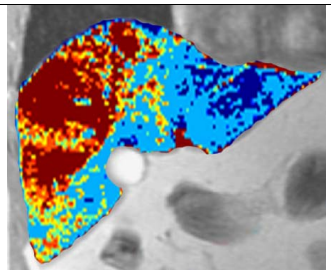


Figure 4 - Example of liver heterogeneity. Although the histopathological result defined the liver as grade 2, the visible grades range from 0 - 3.

Discussion We found a strong agreement between imaging and histopathological results and between the steatosis severity and heterogeneity assessments of the two readers. Since liver biopsy samples a very small portion of the liver and steatosis is frequently a heterogeneous process, such a technique is unlikely to represent a dependable gold standard of the state of the entire liver. The small histopathological sampling of such a heterogeneous disease process may have negatively contributed to the correlation between observed SI loss and that of histopathology. One of the limitations of this study is the narrow range of percent SI loss signifying grade 2 steatosis. This also could have caused a reduction in the ability to correctly grade liver steatosis with SI loss. A second limitation is the lack of T2* correction, however the subjects studied were not considered to be at risk for liver iron deposition. Regardless, results are very promising. MRI may still be a more realistic determinant of disease extent. Further investigation into this technique could offer a rapid, easy to interpret, noninvasive, and more comprehensive approach to accurate steatosis severity and heterogeneity assessment than a single liver biopsy.

References 1. D Priess, N Sattar. Clin Sci 2008; 115(5): 141-50. 2. S R. Mehta, et al. W. J. of Gastroenterology. 2008 14(22): 3476-3483 3. M Bahl, et al. Radiology. 2008 249(1): 160-6. 4. A Qayyum, et al. Radiology. 2005. 237(2): 507-11.

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