Histogram analysis of hepatocellular phase MR imaging as a quantitative value for hepatic fibrosis: preliminary observations

Poster No.: C-0464
Congress: ECR 2012
Type: Scientific Paper
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Keywords: MR, Liver
DOI: 10.1594/ecr2012/C-0464

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Purpose

The diagnosis of liver fibrosis and cirrhosis in patients with chronic liver disease is critical, as cirrhotic patients are at higher risk of developing endstage liver disease, portal hypertension, and hepatocellular carcinoma (HCC) (1,2). These sequelae are important causes of morbidity, mortality, and increasing health care costs (3,4). The cumulative incidence of hepatocellular carcinoma is significantly higher in patients with severe fibrosis than in those with no or mild fibrosis (5). Thus, the early detection and accurate staging of hepatic fibrosis or cirrhosis has become a critical issue in practice.

MR imaging has emerged as a promising modality for the assessment of diffuse liver disease. MR imaging provides excellent tissue contrast and high sensitivity to the effect of contrast agent (6-8), allowing for visualization of hepatic texture that offers the potential of noninvasively diagnosing cirrhosis. Previous studies have reported that fibrosis grades can be accurately assessed using superparamagnetic iron oxides (SPIO) or double contrast material (SPIO plus gadolinium chelates) enhanced MR imaging (9,10). Gadoxetate disodium is an MR imaging contrast agent that was developed for evaluating the hepatobiliary system (11,12). After intravenous injection, gadoxetate disodium is gradually taken up by hepatocytes and is eventually excreted via the biliary system (11). It is known that after gadoxetate is intravenously injected, it accumulates in hepatocytes and cause T1 shortening, which increases liver signal intensity (13). In patients with fibrosis, gadoxetate disodium accumulates and causes T1 shortening preferentially in the spared liver parenchyma, resulting in fibrotic bands appearing relatively hypointense (14,15). For this reason, it may be possible to diagnose cirrhosis on gadoxetate-enhanced MR images on the basis of hepatic texture alterations.

The histogram is a useful tool in hepatic texture analysis (TA) (16,17), providing tool to determine the distribution of the signal intensity levels. We postulated that cirrhotic liver would show wider range of signal intensity values than normal liver on hepatocellular phase MR imaging due to fibrotic bands. To our knowledge, there have not been studies exploring cirrhosis with histogram of hepatocellular phase images using gadoxetate disodium-enhanced MR imaging. The purpose of this study was to investigate whether the histogram analysis of hepatocellular phase MR imaging could be used as a quantitative index for determination of the hepatic fibrosis.
Methods and Materials

Patients

This retrospective study was compliant with the Health Insurance Portability and Accountability Act and was approved by our institutional review board; the need for patient informed consent was waived. From April 2008 to February 2011, 285 patients who were suspected of having chronic liver disease or focal hepatic lesions clinically or at previously performed ultrasonography or computed tomography underwent gadoxetate (Eovist and Primovist, Bayer Healthcare Pharmaceuticals) enhanced liver MRI. Among them, 128 patients were examined with 3T MR scanner. Sixty-five patients were excluded for the following reasons: hepatectomy (n=11); poor biliary excretion (n=9); metastatic disease (n=45).

Finally, a total of 63 patients (28 men, 35 women; age range, 21-90 years), including 37 patients with cirrhosis and 26 patients without liver disease, comprised the study cohort. Patients with suspected benign focal liver lesions in normal liver parenchyma were classified into a normal liver function (NLF) group (n=26). Patients with cirrhosis were classified into a cirrhotic group (n=37). The cirrhotic group (mean age, 56.7 years; range, 22-90 years) included 22 men (mean age, 59.7 years; range, 34-90 years) and 15 women (mean age, 52.4 years; range, 22-72 years), and NLF group (mean age, 47.7 years; range, 21-73 years) included 6 men (mean age, 57.7 years; range, 36-73 years) and 20 women (mean age, 44.7 years; range, 21-63 years).

The most common etiologies of liver disease were hepatitis C, hepatitis B, and alcohol consumption (Table 1). The clinical diagnosis of liver cirrhosis was obtained by previous histologic examination or was clinically apparent (history, laboratory data, imaging study, etc). All NLF and cirrhotic groups underwent standard clinical biochemical testing before the MR examination. Patients with cirrhosis (n=37) were classified into 2 groups according to Child-Pugh classification: a liver cirrhosis with Child-Pugh A group (n=33); and a liver cirrhosis with Child-Pugh B group (n=4). No patients showed liver cirrhosis with Child-Pugh C. Laboratory data (bilirubin, albumin, prothrombin time) of NLF and cirrhotic group are summarized in Table 2.

The NLF group comprised patients with suspected benign focal liver lesions (eg. hemangioma or cyst) in normal liver parenchyma. Patients of NLF group had hemangiomas (n=11), focal nodular hyperplasia (FNH; n=9), cholangitis (n=4), and cysts (n=2). Clinical reference standard and control subjects.- Consecutive patients who met the following criteria were included as control subjects: gadoxetate-enhanced MR imaging performed during the study period for indications other than hepatocellular carcinoma surveillance or diffuse liver disease assessment; no documentation of active or past liver disease; no risk factors for liver disease (ie, consumption of two or more alcoholic drinks daily, viral hepatitis, and/or drug abuse); normal liver function test results obtained within 3 months of the index MR examination; and negative viral serology test
results (if available). Based on these criteria, we judged that focal lesions did not influence liver function in these cases.

**MR Imaging Technique**

MR imaging was performed by using a 3T system (Signa Excite HD; GE Medical Systems, Milwaukee, Wis) with an eight-channel torso coil. The basic MR imaging protocol consisted of the following imaging sequences: breath hold two-dimensional dual echo axial T1-weighted sequence (in-phase and out-of-phase; repetition time msec/echo time msec, 150/4.2 [in phase] and 150/2.0 [out-of-phase]); respiratory-triggered two-dimensional fat-suppressed axial T2-weighted fast spin-echo imaging (1200/72 [effective]); and breath-hold gadoxetate disodium-enhanced hepatic arterial dominant, portal venous, and late dynamic phase imaging with a fat suppressed three-dimensional gradient echo sequence (3.0/1.4; field of view, 24-30 × 32-40 cm; image matrix, 320 × 224; flip angle, 15#; section thickness, 3.0-mm section thickness, with no gap; acquisition time, 90 sections per each phase during 11-second breath hold). Hepatocellular phase imaging was performed with identical MR imaging parameters, except that the acquisition time was of 90 sections during a 22-second breath hold), and the time was within 15-25 minutes (mean, 20.5 minutes) after an intravenous bolus injection of gadoxetate disodium, 0.025 mmol per kilogram of body weight.

**Quantitative Analysis**

MR images were stored in digital imaging and communications in medicine (DICOM) format. Images were reviewed by one abdominal radiologist (J.C.) whether there are typical features of liver cirrhosis several morphologic changes including enlargement of the caudate lobe and the left lateral segment of the liver, atrophy of the right hepatic lobe and the left medial segment, nodularity of the liver surface, coarse liver architecture, ascites, splenomegaly, and the development of collaterals. The same radiologist selected circular, 2 cm² regions of interest (ROI), avoiding vessels and bile ducts. For each patient, images with circular ROIs were stored on a secondary console containing the Osirix Digital Imaging and Communications in Medicine viewer for Macintosh (Osirix, version 3.5.1; the Osirix Foundation, Geneva, Switzerland). Two ROIs were selected in each image from the right hepatic lobe and two ROIs from lateral/medial segments of the left hepatic lobe at the level of horizontal portion of right portal vein. If the ROIs were settled, the standard deviation (SD) and mean values within the ROIs were calculated automatically in the viewer. Signal-to-noise ratios (SNRs) of the liver on hepatocellular phase MRI scans were calculated as follows: liver SNR = liver signal intensity (SI) / SD of background noise. The four ROIs were used to generate quantitative measurements of liver texture heterogeneity-specifically, SD and coefficient of variance (CV) (Figure 1).

The CV for the standard liver region of interest was calculated as follows: $CV = \frac{SD_{\text{liver}}}{SI_{\text{liver}}}$, where $SD_{\text{liver}}$ is the standard deviation of the mean liver parenchyma signal.
intensity and $SI_{\text{liver}}$ is the mean signal intensity of the liver parenchyma. Based on our observation that fibrotic liver has a more heterogeneous texture (hypointense reticulations against a bright liver background) than does the homogeneous normal liver, the CV was used as a measure of regional liver texture heterogeneity. Because image noise contributed to the variance in liver signal intensity, we also calculated a corrected CV ($CV_{\text{corr}}$) by subtracting the standard deviation of the mean air signal intensity from the standard deviation of the mean liver parenchyma signal intensity in the numerator: $CV_{\text{corr}} = (SD_{\text{liver}} - SD_{\text{air}})/SI_{\text{liver}}$ (15).

**Statistical Analysis**

Data distributions were tested for normality with Shapiro-Wilk tests. A comparison of $SI_{\text{liver}}$, $SD_{\text{liver}}$, CVs, and corrected CVs of the groups was carried out using the unpaired Student $t$-test. The Spearman's correlation test was used to assess the correlation of CV and corrected CV between NLF and cirrhotic groups. The optimal cut-off values of CVs for distinguishing normal and cirrhotic groups were calculated. The analysis was performed using SPSS (17.0, SPSS Inc, Chicago, IL, USA). A $p$ value <0.05 was considered significant.
Table 1. Causes of Liver Disease

<table>
<thead>
<tr>
<th>Cause</th>
<th>No. of Patients*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis C virus</td>
<td>14 (37)</td>
</tr>
<tr>
<td>Hepatitis B virus</td>
<td>8 (22)</td>
</tr>
<tr>
<td>Alcohol intake</td>
<td>5 (14)</td>
</tr>
<tr>
<td>Nonalcoholic steatohepatitis</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Recurrent pyogenic cholangitis</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Cryptogenic</td>
<td>4 (10)</td>
</tr>
</tbody>
</table>

*Numbers in parentheses are percentages

Table 1

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Table 2. Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>NLF Group (n=26)</th>
<th>Cirrhosis Group (n=37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>47.7</td>
<td>56.7</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>0.56 ± 0.3</td>
<td>1.0 ± 0.7</td>
</tr>
<tr>
<td>Albumin (mg/dL)</td>
<td>4.37 ± 0.3</td>
<td>4.0 ± 0.6</td>
</tr>
<tr>
<td>Prothrombin time (second)</td>
<td>12.2 ± 1.0</td>
<td>12.9 ± 1.5</td>
</tr>
</tbody>
</table>

NLF= normal function liver

Values indicate mean ±1 standard deviation.

INR indicates international normalized ratio.

Table 2

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Fig. 1: Different histograms of normal function liver and cirrhotic liver on hepatocellular phase. (a) Axial T1-weighted hepatocellular phase image obtained after injection of gadoxetate disodium in a 56-year-old woman with normal function liver and coefficient of variance (CV) value of 0.035. (b) Histogram of selected region of interest (ROI) on hepatocellular phase image shows narrow distribution. (c) Axial T1-weighted hepatocellular phase image obtained after injection of gadoxetate disodium in a 48-year-old man with cirrhosis and coefficient of variance (CV) value of 0.062. (d) Histogram of selected region of interest (ROI) on hepatocellular phase image shows wide distribution.

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Results

Of 37 cirrhotic patients, 35 patients showed the definite morphological changes of cirrhosis on visual evaluation. The mean pixel size of NLF group (0.64 mm × 0.42 mm) was comparable to cirrhotic group (0.63 mm × 0.41 mm) \((p>0.05)\). The mean signal intensity ± SD of NLF group was 4146.7 ± 167.0 (maximum value 10715.3; minimum value 374.8) while that of cirrhotic group was 1960.6 ± 143.5 (maximum value 11065.9; minimum value 216.1). There was no statistical significance of the liver SNR between normal group and cirrhotic group (mean SNR ± SD; 37.10 ± 12.7 for NLF group and 32.34 ± 15.3 for cirrhosis group, \(p=0.184\)).

The mean SI, SD, CV, and corrected CV of NLF and cirrhotic groups are shown in figure 2-4. The SD was 167.0 ± 142.1 (mean SD ± SD) in the NLF group and 143.5 ± 202.2 in cirrhotic group. There was no statistical significance of SD between NLF and cirrhotic group \((p=0.307)\). In the NLF group, the CV value was 0.041 ± 0.009 (mean CV ± SD; maximum value 0.08; minimum value 0.03). In the cirrhotic group, the CV value was 0.071 ± 0.020 (mean CV ± SD; maximum value 0.17; minimum value 0.03). The CV values of cirrhotic group were significantly higher than NLF group \((p<0.001)\). The CV for NLF and cirrhotic groups showed nonnormal distribution \((p<0.05, \text{Shapiro-Wilk tests})\), showing skewness of 1.11 and 0.94, respectively (Fig. 5,6). The more skewed data for NLF group than cirrhotic groups might be explained by inhomogeneous group of patients. The kurtosis of NLF group was 2.03 while that of cirrhotic group was 1.95. The Spearman's correlation test indicated that CV values were strongly correlated with the presence of cirrhosis with a value of 0.729 \((p<0.001)\). The corrected CV values of cirrhotic group were also higher than NLF group \((0.468 ± 0.20 \text{ vs } 0.349 ± 0.22)\) \((p<0.001)\).

Sensitivities and specificities at various CV values were calculated for distinguishing normal from cirrhotic group (Table 3). Cut-off value of CV to distinguish normal from cirrhotic group with best accuracy was 0.052 (sensitivity 83.8% and specificity 88.5%).
Fig. 2: Box plot shows results of analysis of (a) the standard deviation, (b) CV values, and (c) corrected CV for NLF and cirrhotic group. Each box stretches from the 25th percentile at lower edge to the 75th percentile at upper edge; the median is shown as a line across the box. There are two adjacent values below and above the box: The largest value is below the upper inner limit and the smallest value is above the lower inner limit. Outside values below or above the inner limit but within the outer limit are outliers. Note. Mean SI= mean signal intensity, SD=standard deviation, CV=coefficient of variation, NLF= normal liver function.
Fig. 3

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Fig. 4
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Fig. 5: Histogram of NLF and cirrhosis groups. The CV for NLF group showed a normal distribution, showing a skewness value of 1.11. The CV for cirrhosis group showed a normal distribution, showing a skewness value of 0.94. Note. CV= coefficient of variation.

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Fig. 6

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<table>
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<tr>
<th>Cut-off values</th>
<th>0.03</th>
<th>0.04</th>
<th>0.05</th>
<th>0.052</th>
<th>0.06</th>
<th>0.07</th>
<th>0.08</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>99.3</td>
<td>98.0</td>
<td>88.5</td>
<td>83.8</td>
<td>68.9</td>
<td>44.6</td>
<td>27.0</td>
</tr>
<tr>
<td>Specificity</td>
<td>9.6</td>
<td>55.8</td>
<td>78.8</td>
<td>88.5</td>
<td>95.2</td>
<td>99.0</td>
<td>99.0</td>
</tr>
</tbody>
</table>

Values of sensitivity and specificity indicate percentage (%).

Note that a cut-off value of 0.052 yields sensitivity 84% and specificity 89%.

**Table 3**

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Conclusion

Our results suggest that histogram analysis of hepatocellular phase MRI can be helpful for differentiating patients with normal liver function and those with cirrhosis. Among the parameters of histogram, the CV values of histogram were significantly different between NLF and cirrhotic groups. Our study suggests that histogram analysis has the potential to provide quantitative index of liver cirrhosis. Cirrhosis induces several morphologic changes including enlargement of the caudate lobe and the left lateral segment of the liver, atrophy of the right hepatic lobe and the left medial segment, nodularity of the liver surface, coarse liver architecture, ascites, splenomegaly, and the development of collaterals (18-21). However, most are based on morphologic changes in the liver that occur late in progression of liver disease or secondary signs of portal hypertension. These findings have limited utility for the detection of early cirrhosis and the grading of advanced fibrosis. The diagnosis of hepatic fibrosis of an intermediate degree is difficult because hepatic parenchymal textural alterations are often subtle. Although there is overlap of CV values between the NLF and cirrhotic groups, we were able to reliably differentiate the two groups with the CV of hepatocellular phase imaging. Our study also introduces a simple and practical method to determine the distribution of pixel values. The SD and average value of ROIs can be measured in PACS and the CV can be easily calculated. Therefore the CV of hepatocellular phase could be used as a screening measurement tool for evaluating hepatic parenchymal texture and aid in the diagnosis of cirrhosis in daily practice.

The histogram is a graphical representation showing a visual impression of the distribution data (16,17). The histogram is installed in the PACS program which makes it possible to assess the distribution of each pixel value. In PACS, the signal intensity value within the ROI is shown on the monitor by an automatic calculation of the selected ROI. The histogram illustrates how the pixels in an image are distributed by graphing the number of pixels, and the SD represents the variation in the signal intensity values. The vertical axis shows the total number of pixels with a given value. The CV is a normalized measure of dispersion of a probability distribution that can be used when comparing between data sets with different units or widely different means. The CV values of hepatocellular phase of gadoxetate disodium-enhanced MRI that are calculated on the ROI histogram reflect the homogeneity or heterogeneity of the hepatic parenchyma. Smaller CV values are thought to represent normal liver while larger CV values reflect the possibility of cirrhotic liver in which with fibrotic bands are thought to cause reflections of various signal intensities. Although differences in the CV values between NLF and cirrhotic groups were observed, there was definite overlap of CV values between NLF and cirrhotic groups. This was presumably because variable stages of fibrosis were included in this study and small vessels or bile ducts could be included in the ROIs. The evaluation of fibrosis, therefore, depends on the choice of ROI, which should be improved in the future.
In conclusion, the histogram analysis of hepatocellular phase MRI reflects the homogeneity or heterogeneity of the hepatic parenchyma. The CV values of histogram on hepatocellular phase can be used as a quantitative value that can determine the hepatic fibrosis.
References


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