

Evaluation of Fibrosis in Liver Cirrhosis by Superparamagnetic Iron Oxide (SPIO)-Enhanced MR Imaging: Does the Radiological Non-Invasive Fibrosis Index Correlate with the Laboratory Non-Invasive Fibrosis Index?

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Purpose : To evaluate the correlation between the radiological non-invasive hepatic fibrosis index (RNHFI), as determined by SPIO-enhanced MRI, and the laboratory non-invasive hepatic fibrosis index.

Materials and Methods : Patients (99 total: 61 men and 38 women; mean age: 58 years) who underwent SPIO-enhanced MRI (1.5T) during 5 years included. These patients were subdivided into a liver cirrhosis group (LCG) and a non-liver cirrhosis group (non-LCG). Using PACS view, we measured the RNHFI (mean standard deviation of hepatic signal intensity (SD), noise-corrected coefficient of variation (CV)) of three ROIs in the liver parenchyma by SPIO-enhanced MRI. The laboratory non-invasive hepatic fibrosis index (AST-platelet ratio index (APRI)) of all patients was calculated from the laboratory data. We compared the RNHFI and APRI of LCG with those of non-LC group using Student's t-test. A bivariate correlation was performed to investigate the relationship between the RNHFI and APRI in the LCG.

Results : For the LCG, mean values of SD and CV by SPIO-enhanced MRI were 10.3 ± 3.7 and 0.19 ± 0.08 , respectively. For the non-LCG, mean values of SD and CV were 6.5 ± 1.6 and 0.08 ± 0.05 , respectively. The mean APRI of the LCG and the non-LCG were 2.04 ± 1.7 and 0.32 ± 0.32 , respectively. The RNHFI and APRI were significantly different between both groups ($p < 0.05$). For the LCG, the bivariate correlation between SD and APRI revealed a statistically significant positive correlation ($r = 0.5$, $p < 0.001$). In both groups, there was no statistically significant correlation between CV and APRI.

Conclusion : A measurement of SD can be a simple and useful method for the evaluation of hepatic fibrosis.

Index words : Liver, Fibrosis, Cirrhosis, MRI,
SPIO, superparamagnetic iron oxide

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Introduction

Hepatic fibrosis is an important cause of morbidity, mortality, and increasing health care costs (1, 2). Mortality associated with hepatic fibrosis results mainly from the development of liver cirrhosis associated with complications such as hepatocellular carcinoma or GI bleeding. In assessing hepatic fibrosis, liver biopsy is currently the gold standard. However, a liver biopsy is expensive and has inborn risks (3). And, because only 1/50000 of the liver is sampled, there could be sampling error (4). Furthermore, inter- and intra-observer discrepancies of 10% to 20% in assessing hepatic fibrosis have been reported, which may result in the understaging of liver cirrhosis (5). Therefore, there has been a need to develop accurate and reliable non-invasive methods to assess the hepatic fibrosis. An ideal non-invasive diagnostic method for hepatic fibrosis should be simple, easily available, inexpensive, and accurate.

In chronic hepatitis patients, non-invasive approaches to the assessment of histology include clinical symptoms and signs, routine laboratory tests, serum markers of fibrosis and inflammation, quantitative assays of liver function, and radiological imaging studies (6, 7). However, for the prediction and diagnosis of hepatic fibrosis, the sensitivity and specificity of these laboratory and radiological imaging findings are generally poor, especially in patients with milder liver fibrosis.

Many studies have been performed to evaluate the use of readily available laboratory test results as predictors of significant hepatic fibrosis in patients with chronic hepatitis. Wai et al. devised an index, called the AST to platelet ratio index (APRI), and showed that the APRI can predict significant hepatic fibrosis or cirrhosis in patients with chronic hepatitis C with a high degree of accuracy (8). According to another recent study by Sim et al., the APRI is the most accurate laboratory index in predicting severe hepatic fibrosis and cirrhosis in patients with chronic hepatitis B (9).

Recently, the possibility of non-invasively diagnosing cirrhosis on the basis of the hepatic texture alterations seen on superparamagnetic iron oxide (SPIO)-enhanced MR images has been suggested (10). After SPIOs are injected intravenously, hyper-intense reticulations,

which are postulated to represent septal fibrosis, may be seen in the cirrhotic liver. It is known that intravenously infused SPIOs accumulate in liver reticuloendothelial cells and cause T2* shortening, which reduces hepatic signal intensity (11). In patients with hepatic fibrosis and cirrhosis, SPIOs accumulate and cause T2* shortening in the spared liver parenchyma, which leads to fibrotic bands of relatively high signal intensity.

The aim of this study was to evaluate the correlation between the radiological non-invasive hepatic fibrosis index (RNHFI) as determined by SPIO-enhanced MRI and APRI in patients with liver cirrhosis.

Materials and Methods

Patients

This was a retrospective study approved by the Institutional Review Board. The study sample consisted of consecutive patients who had undergone SPIO-enhanced MR imaging between December 2003 and March 2007 at our institution. We retrospectively reviewed radiology and hepatology records to divide these patients into a liver cirrhosis group (LCG) and a non-LC group (non-LCG). The information collected included demographic data, dates of SPIO-enhanced MR imaging, liver disease history, cause, risk factors, hepatitis viral serology, and serum liver function test results. The presence of cirrhosis was confirmed on the basis of liver surface nodularity, hypertrophy of left hepatic lobe, and portal hypertension stigmata (i.e., ascites, varices, and/or splenomegaly) by using ultrasonography (US), computed tomography (CT), and magnetic resonance (MR) imaging. Liver disease history, hepatitis viral serology, and serum liver function test results were also considered for the diagnosis of liver cirrhosis.

In most non-LCG patients, SPIO-enhanced MR imaging was performed to evaluate for metastatic hepatic tumor, and patients with a hepatitis background were excluded from the non-LCG. Patients with ambiguous liver cirrhosis were excluded from the LCG. Patients with a large hepatic tumor replacing a large portion of the hepatic parenchyma were excluded from this study.

Imaging protocol

All MR imaging was conducted using a 1.5 T (Magnetom Symphony; Siemens, Erlangen, Germany) with a combination of a phased array body coil and a spine array coil for signal reception. The imaging protocol for each patient included a respiratory-triggered T2-weighted turbo spin echo sequence (TR/TE of 3300–4200/76, an echo train length of 13, a 150° flip angle, a matrix of 202 × 384), a breath-hold T2*-weighted gradient recalled-echo (GRE) sequence (TR/TE of 180/12, a 30° flip angle, a matrix of 144 × 256, and two acquisitions), a breath-hold T2-weighted turbo spin-echo sequence (TR/TE of 2500/103, a 140° flip angle, a matrix of 202 × 320, a 5 mm slice thickness), HASTE sequence (TR/TE of 400/146, a 150° flip angle, a matrix of 166 × 256, a 3 mm slice thickness), and a breath-hold T1-weighted fast low-angle shot (FLASH) sequence (TR/TE of 159/2.7, a 70° flip angle, a matrix of 144 × 256, a signal average of one, and two acquisitions).

The SPIO-enhanced MRI was comprised of the respiratory-triggered T2-weighted TSE sequence, the breath-hold T2*-weighted GRE sequence, a breath-hold T2-weighted TSE sequence, a HASTE sequence for the baseline MRI, and a double-echo chemical shift gradient-echo sequence (TR/first echo TE, second echo TE, 180/2.4 [opposed-phase], 5.2 [in-phase]; flip angle, 70°). The SPIO was rapidly injected intravenously through a 5- μ m filter and followed by flushing 20-mL of saline. Imaging commenced approximately 10 min after the intravenous injection of contrast agent.

Radiological non-invasive hepatic fibrosis index and APRI

Two radiologists retrospectively reviewed, in consensus and in random order, all MR images on two side-by-side 2048 × 2560-pixel-resolution gray-scale picture archiving and communicating system monitors (Barco, Belgium). The radiologists were blinded to the demographic, clinical, laboratory, and pathology data at the time of the image review, which was performed a minimum of 4 weeks after patient data collection. Liver dysmorphism, liver surface nodularity, and portal hypertension stigmata (ie, ascites, varices, and/or splenomegaly) were considered signs of liver cirrhosis.

We randomly selected 3 random areas, one from the left lobe and two from the right hepatic lobe, that

didn't show artifact on T2*-weighted GRE sequence. Then, by using the method of Aguirre et al (12), three regions of interest were placed in the liver parenchyma on each section at similar distances from the phased-array coils. Liver regions of interest were chosen to avoid visible blood vessels, bile ducts, and prominent artifacts. Another three ROIs were placed in the air to the right and left of the abdominal wall on the same section. All regions of interest were similar in size (90~120 mm²) and shape (round). Using the picture archiving and communication system software (PiViewSTAR, Infinitt, Seoul, Korea), we measured the mean of the standard deviation of hepatic signal intensity (SD) from three ROIs in the liver parenchyma on SPIO-enhanced MRI. According to a study by Aguirre et al. (12), because image noise contributes to the variance in liver signal intensity, the corrected coefficient of variation is the most meaningful measure of liver texture heterogeneity. Thus, we also measured the corrected coefficient of variation (CV) from ROIs of the liver parenchyma and air, as follows: $CV = (SD - SD_{air}) / SI_{liver}$, where SD is the mean standard deviation of hepatic signal intensity, SD_{air} is the standard deviation of the mean air signal intensity, and SI_{liver} is the mean signal intensity of the liver parenchyma (Fig

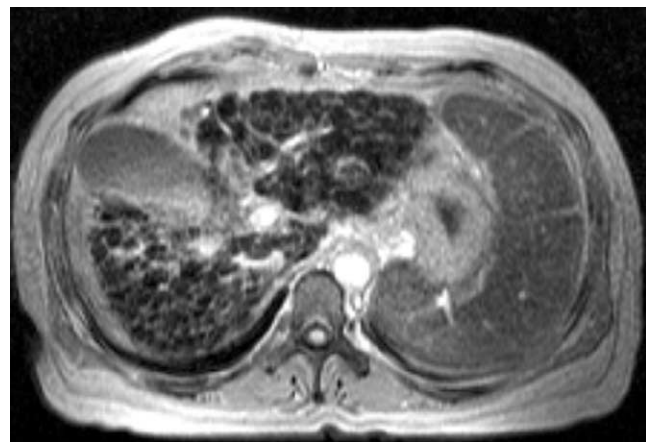


Fig. 1. Measurement of SD and CV. A 39-year-old woman with hepatitis B in the LCG. Post-superparamagnetic iron oxide (SPIO) T2*-weighted gradient-recalled-echo (GRE) image shows a reticulation pattern involving the whole liver. On this section, two regions of interest (ROIs) are seen in the liver parenchyma and the air. The mean signal intensity of the liver parenchyma was 44.87. The mean standard deviation of the liver parenchyma and the air were measured to be 17.8 and 5.2, respectively. Using these data, the CV was calculated to be 0.28 ($= (17.8 - 5.2) / 44.87$).

1).

We calculated the APRI of all patients from the laboratory data as follows: $APRI = \frac{AST \text{ level (upper limit of normal)}}{\text{platelet counts (10}^9\text{/L)}} \times 100$. We also evaluated the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of APRI, using 2 cut-off values suggested by previous studies of Wai et al. (8) and Sim et al. (9) to predict the existence of liver cirrhosis.

We compared the RNHFI and APRI of the LC group with those of the non-LC group using Student's t-test. A bi-variate correlation was performed to investigate the relationship between the RNHFI and APRI.

Results

A total of 99 patients were included in this study. Sixty-one (61.6%) were men, and 38 were women (38.4%). The mean age of the 99 patients was 57.4 ± 10.8 years.

Fifty patients were divided into the LCG, 35 (70%) were men and 15 (30%) were women. The mean age of the LCG was 55.2 ± 9.48 years. Forty-nine patients were divided into the non-LCG, 26 (53.1%) men and 23 (46.9%) women. The mean age of the non-LCG was 59.7 ± 11.7 years (Table 1).

The most common cause of liver disease was

hepatitis B (37 patients; 74%). Other causes of liver disease were hepatitis C (7 patients; 14%), chronic alcoholism (5 patients; 10%). One patient (2%) had cryptogenic liver cirrhosis (Table 2).

In the LCG, the mean values of AST and platelets were 59.3 ± 48.8 and 87.9 ± 39.4 , respectively. In the non-LCG, the mean values of AST and platelets were 26.1 ± 17.8 and 240 ± 59.1 , respectively. The mean APRI of the LCG and the non-LCG were 2.04 ± 1.7 and 0.32 ± 0.32 , respectively. In the LCG, the mean values of SD and CV by SPIO-enhanced MRI were 10.3 ± 3.7 and 0.19 ± 0.08 , respectively. In the non-LCG, the mean values of SD and CV were 6.5 ± 1.6 and 0.08 ± 0.05 , respectively.

The SD, CV, and APRI of the LCG were significantly higher than those of the non-LCG ($p < 0.05$) (Table 1). In the LCG, SD and APRI were significantly correlated ($r = 0.5$, $p < 0.001$). CV and APRI were not significantly correlated. In the non-LCG, SD and APRI were not significantly correlated. CV and APRI were not also significantly correlated. For all patients, SD and APRI were significantly correlated ($r = 0.633$, $p < 0.001$); CV and APRI were also significantly correlated ($r = 0.438$, $p < 0.001$) (Fig. 2, 3).

When a cut-off APRI value of 1.5 was chosen for the prediction of cirrhosis, the sensitivity, specificity, PPV, and NPV were 48%, 98%, 96%, and 65%, respectively. When a cut-off APRI value of 2 was chosen for prediction of cirrhosis, the sensitivity, specificity, PPV,

Table 1. Characteristics of the Study Population (n=99)

	LCG (n=50)	non-LCG (n=49)
Age (years)	55.2 ± 9.48	59.7 ± 11.7
AST (IU/L)	59.3 ± 48.8	26.1 ± 17.8
Platelets ($\times 10^9$ /mL)	87.9 ± 39.4	240 ± 59.1
APRI	2.04 ± 1.7	0.32 ± 0.32
SD	10.3 ± 3.7	6.5 ± 1.6
CV	0.19 ± 0.08	0.08 ± 0.05

Note.— LCG = Liver cirrhosis group, AST = Aspartate aminotransferase, APRI = AST-platelet ratio index, SD = Standard deviation, CV = noise-corrected coefficient of variation

Table 2. Causes of Liver Cirrhosis (n=50)

Cause	No. of patients
HBV	37 (74%)
HCV	7 (14%)
Alcohol	5 (10%)
Cryptogenic	1 (2%)

Note.— HBV = Hepatitis B virus, HCV = Hepatitis C virus



Fig. 2. 53-year-old man in the non-LCG. Post-superparamagnetic iron oxide (SPIO) T2*-weighted gradient-recalled-echo (GRE) image shows homogeneity of signal intensity in the liver parenchyma. SD, CV and APRI were measured to be 6.2, 0.076, and 0.16, respectively.

and NPV were 40%, 100%, 100%, and 62%, respectively (Table 3).

Discussion

Progressive hepatic fibrosis leading to the development of liver cirrhosis is a feature of almost all chronic liver diseases. Recently, considerable progress has been achieved in understanding of the pathophysiology of extracellular matrix (ECM) deposition and metabolism. It is clearly known that ECM metabolism is a dynamic process and that the deposition of ECM is more reversible than previously thought. The hepatic stellate cell is a main source of ECM deposition and plays a key role in liver fibrosis (1).

Laboratory findings of hepatic fibrosis include a decrease in albumin level, an increase in bilirubin

level, an extension of prothrombin time, a increase in the aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio, and a decrease in WBC and platelet counts. However, these laboratory finding show disappointing sensitivity or specificity in predicting and diagnosing hepatic fibrosis or liver cirrhosis. According to studies by Wai et al. and Sim et al., the APRI is the most accurate laboratory index in predicting severe hepatic fibrosis in patients with chronic hepatitis B and C (8, 9).

Conventionally, imaging evaluation of hepatic fibrosis has been limited to the assessment of cirrhosis-related complications. Although the presence of cirrhosis can be confirmed on the basis of liver contour abnormalities and portal hypertension stigmata by using US, CT, and MR imaging, these findings are generally insensitive to the detection of milder liver fibrosis (13, 14).

Several non-invasive alternatives to liver biopsy have been studied for staging liver fibrosis. Serum tests include measurement of specific markers of fibrosis, such as hyaluronic acid and N-terminal collagen III propeptide, which are products of the degradation or synthesis of the ECM (15). Because fibrosis is not specific to the liver, the usefulness of these markers is limited. The use of more comprehensive biomarkers based on proteome or glycome fingerprints has been proposed (16). However, these methods are expensive and are not readily available.

Scoring systems, such as the FibroTest (Biopredictive, Paris, France), have also been proposed. These serum tests use biochemical markers that have indirect relationship with fibrosis and use a purely statistical approach to staging the liver fibrosis. Previous studies showed that serum scoring systems can differentiate accurately only minimal and advanced fibrosis among the hepatic fibrosis spectrum (17). Moreover, some

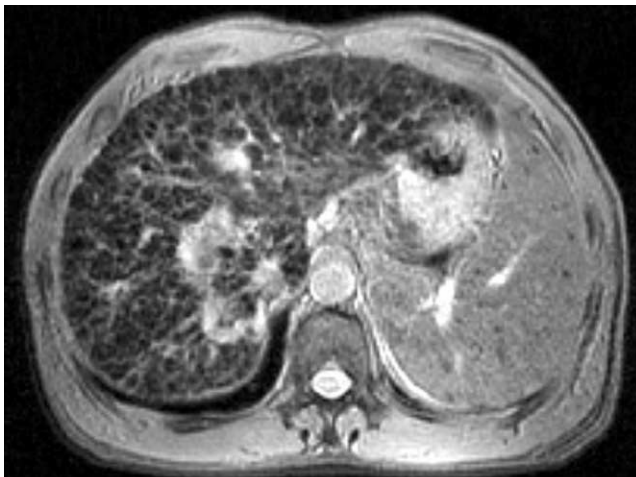


Fig. 3. 56-year-old man with hepatitis B in the LCG. Post-superparamagnetic iron oxide (SPIO) T2*-weighted gradient-recalled-echo (GRE) image shows the reticulation pattern involving the whole liver. Splenomegaly is also seen. SD, CV, and APRI were measured to be 9.2, 0.141, and 2.45, respectively.

Table 3. Accuracy of APRI in Predicting Cirrhosis

APRI	All patients (n = 99)	LCG (n = 50)	Non-LCG (n = 49)	Sensitivity %	Specificity %	PPV %	NPV %
≤ 1.50	74	26	48	48	98	96	65
> 1.50	25	24	1				
≤ 2.0	79	30	49	40	100	100	62
> 2.0	20	20	0				

Note.— APRI = AST-platelet ratio index, LCG = Liver cirrhosis group, PPV = Positive predictive value, NPV = Negative predictive value

parameters can be influenced by extrahepatic diseases.

Transient elastography (FibroScan; Echosens, Paris, France) is a non-invasive and reproducible method to assess liver fibrosis, by measuring liver stiffness. Its diagnostic performance is similar to that of methods based on serologic markers. Castera et al. suggested that the combined use of FibroScan and FibroTest could be an alternative to a liver biopsy in patients with chronic hepatitis C (18). However, liver stiffness measurements can be impossible in obese patients, those with a narrow intercostal space, and patients with ascites.

Magnetic resonance elastography is also a non-invasive method of measuring the viscoelastic properties of the liver. Preliminary reports suggest that MR elastography is a feasible method for staging liver fibrosis. The results of a study by Huwart et al. show that MR elastography is an accurate non-invasive method of staging liver fibrosis and is superior to scoring system using biochemical markers (19). However, MR elastography is expensive and not readily available.

Several other imaging methods including double contrast material-enhanced MR imaging, perfusion MR imaging, and diffusion MR imaging have also been used to diagnose and stage liver fibrosis. However, most of these methods are limited to the detection of advanced fibrosis (12, 20).

Superparamagnetic iron oxide particles (SPIO) are reticuloendothelial-specific particulate contrast agents for MR imaging, which markedly shorten T2 and moderately affect T1 relaxation rates. Consequently, the signal intensity of the liver parenchyma decreases on T2-weighted sequences, except in the areas where Kupffer cells are not present, resulting in an increase in the abnormality-to-liver contrast ratio in patients with liver cirrhosis. These findings are especially well observed on gradient-echo images obtained with longer echo times (10).

In our study, APRI showed somewhat lower sensitivity and higher specificity than those of studies by Wai et al. and Sim et al. (8, 9). The possible explanations are that patients with milder liver fibrosis were not included in our study, and that there was no pathologic correlation.

In our study, CV and APRI were not significantly correlated in the LCG. However, for all patients (when

LCG and non-LCG were combined), CV and APRI were significantly correlated ($r = 0.438$, $p < 0.001$). One possible explanation for this is that patients with milder liver fibrosis were not included in this study or that CV is very vulnerable to the standard deviation of the mean air signal intensity.

Usually the standard deviation of the mean air signal intensity is large on a T2*-weighted GRE sequence. In our study, SD showed a better correlation with APRI than with CV. Moreover, the measurement of SD is simpler than the measurement of CV. Thus, we believe that measurement of SD is more useful than measurement of CV in evaluating liver texture heterogeneity.

We acknowledge that there are limitations to our study. First, there was no pathologic correlation. Although liver biopsy is the gold standard for assessing hepatic fibrosis, it is not always available in all patients who are thought to have liver cirrhosis. Furthermore, in many patients with hepatic fibrosis, imaging findings are sufficient to diagnose liver cirrhosis. The second limitation is that all MR studies were performed using a 1.5-T MR system. Therefore, we are not sure that commercially-used 3-T MR systems exhibit the same results as this study. The third limitation is that there was no comparison between SPIO-enhanced T2*-GRE images and Gadolinium-enhanced T1-weighted images. However, double contrast material-enhanced MR imaging with SPIO and Gadolinium is not routinely performed in our institution and is not necessary in all patients with liver fibrosis.

Conclusion

The combined use of a radiological non-invasive hepatic fibrosis index and APRI could help predict the degree of hepatic fibrosis and decrease the need for liver biopsy. In particular, we believe that SD is a more useful index than CV because of its simplicity. However, further prospective studies, including pathologic correlation, are necessary to validate the SD in a larger number of patients with hepatic fibrosis.

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Superparamagnetic Iron Oxide-Enhanced MRI를 이용한 간섬유화의 평가: 영상의학적 비침습적 간섬유화 지표가 AST/혈소판 비와 상관 관계가 있는가?

고려대학교 구로병원 영상의학과

김신기 · 이창희 · 김경아 · 최재웅 · 이종미 · 박철민

목적: SPIO-enhanced MRI상에서 얻은 radiological non-invasive hepatic fibrosis index (RNHFI)와 AST/혈소판 비(AST to platelet ratio index, APRI)간의 상관관계를 알아보고자 하였다.

대상 및 방법: 5년동안 SPIO-enhanced MRI를 시행받은 환자들을 대상으로 하였다. 환자들을 간경변 집단과 비(非)간경변 집단으로 분류했다. PACS를 이용, 각 환자의 SPIO-enhanced MRI에서 RNHFI (간실질 신호강도 표준편차의 평균(SD), 잡음교정 변이계수(CV))를 산출했고, 각 환자의 실험실 검사 결과를 이용, APRI를 산출했다. Student's t-test를 이용하여 두 집단간의 RNHFI와 APRI의 차이를 비교했다. 각 집단에서, RNHFI와 APRI간의 이변량 상관분석을 시행했다.

결과: 간경변 집단에서, SD, CV의 평균은 각각 10.3 ± 3.7 , 0.19 ± 0.08 였다. 비간경변 집단에서, SD, CV의 평균은 각각 6.5 ± 1.6 , 0.08 ± 0.05 였다. 두 집단의 평균 APRI는 각각 2.04 ± 1.7 , 0.32 ± 0.32 였다. RNHFI와 APRI는 두 집단 사이에서 의미 있는 차이를 보였다 ($p < 0.05$). 간경변 집단에서, SD와 APRI는 양의 상관관계를 보였다 ($r=0.5$, $p < 0.001$).

결론: SD값이 간섬유화의 간단하고 유용한 예측 인자가 될 수 있을 것으로 기대된다.

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