Computer-aided assessment of hepatic contour abnormalities as an imaging biomarker for the prediction of hepatocellular carcinoma development in patients with chronic hepatitis C

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\textbf{Article info}

\textbf{Purpose:} To evaluate whether a hepatic fibrosis index (HFI), quantified on the basis of hepatic contour abnormality, is a risk factor for the development of hepatocellular carcinoma (HCC) in patients with chronic hepatitis C.

\textbf{Materials and methods:} Our institutional review board approved this retrospective study and written informed consent was waived. During a 14-month period, consecutive 98 patients with chronic hepatitis C who had no medical history of HCC treatment (56 men and 42 women; mean age, 70.7 years; range, 48–91 years) were included in this study. Gadoxetic acid-enhanced hepatocyte specific phase was used to detect and analyze hepatic contour abnormality. Hepatic contour abnormality was quantified and converted to HFI using in-house proto-type software. We compared HFIs between patients with (\(n=54\)) and without (\(n=44\)) HCC. Serum levels of albumin, total bilirubin, aspartate transferase, alanine transferase, percent prothrombin time, platelet count, alpha-fetoprotein, protein induced by vitamin K absence-II, and HFI were tested as possible risk factors for the development of HCC by determining the odds ratio with logistic regression analysis.

\textbf{Results:} HFIs were significantly higher in patients with HCC (0.58 ± 0.86) than those without (0.36 ± 0.11) (\(P<0.001\)). Logistic analysis revealed that only HFI was a significant risk factor for HCC development with an odds ratio (95% confidence interval) of 26.4 (9.0–77.8) using a cutoff value of 0.395.

\textbf{Conclusion:} The hepatic fibrosis index, generated using a computer-aided assessment of hepatic contour abnormality, may be a useful imaging biomarker for the prediction of HCC development in patients with chronic hepatitis C.

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\section*{1. Introduction}

Chronic hepatitis C is a leading cause of hepatic fibrosis and hepatocellular carcinoma (HCC), both of which serve as major indications for liver transplantation \cite{1,2}. The presence of cirrhosis is highly associated with HCC development in patients with chronic hepatitis C \cite{3,4}. Pathologically, cirrhosis is the end stage of a variety of chronic diffuse liver diseases resulting in numerous nodules and fibrosis \cite{5}. Detection and grading of hepatic fibrosis currently requires a biopsy, which is invasive and may potentially expose patients to a risk of serious complications. Indeed, a study that examined complications associated with over 68,000 percutaneous liver biopsies found a morbidity rate of 3\% and a mortality rate of 0.03\% \cite{6}. Therefore, noninvasive methods, including ultrasonography \cite{7} and MR elastography techniques \cite{8,9}, have been proposed and tested as a means to detect liver cirrhosis. Ultrasonographic features of liver surface nodularity are recognized as reliable predictors of severe liver fibrosis in patients with chronic hepatitis \cite{10,11}. We previously reported a non-invasive computer-aided image analysis of hepatic contours that accurately detected hepatic fibrosis at stages F3 and F4 \cite{12}. Furthering our investigation in this field, we also developed and tested semi-automated computer-aided diagnosis software that was based on the hepatic contour morphological features from MR images to improve the prediction
of HCC development in patients with chronic hepatitis C. Thus, the purpose of this study was to demonstrate the clinical significance of the hepatic fibrosis index (HFI), quantified on the basis of hepatic contour abnormality, for the development of HCC in patients with chronic hepatitis C.

2. Materials and methods

2.1. Patients

Our institutional review board approved this retrospective study and written informed consent was waived. Between February 2012 and February 2013, 422 consecutive patients suspected of having chronic liver disease or focal hepatic lesions clinically or from previously performed ultrasonography or computed tomography (CT), underwent gadoxetic acid enhanced MR imaging in our department. In 188 of the 422 patients, hepatitis C was diagnosed by virus antibody detection. Among the 188 patients with chronic hepatitis C, we retrospectively included 98 patients who had no medical history of HCC treatment (56 men and 42 women; age range, 48–91 years; mean, 70.7 years). Among them, HCCs were identified in 54 patients (31 men and 23 women; age range, 48–91 years; mean, 71.6 years) by definitive surgery (n = 15), tumor biopsy (n = 15), and pathognomonic findings with combination CT hepatic arteriography and CT during arterial portography and lipiodolized CT after transcatheter arterial chemoembolization (n = 24). No HCC was found in the remaining 44 patients (25 men and 19 women; age range, 50–84 years; mean, 69.6 years;), in whom the absence of HCC was confirmed by follow-up gadoxetic acid-enhanced MR imaging performed in the following 3–6 months.

2.2. MR imaging techniques

MR imaging was performed using a 3-T MR system (Intera Achieva Quasar Dual; Philips Medical Systems, Netherlands) with a 6-channel torso array coil. The basic MR imaging protocol consisted of the following: breath-hold two-dimensional dual-echo axial T1-weighted fast field-echo (repetition time [TR]/echo time [TE], 292/2.3 ms at in-phase and 292/1.1 ms at opposed-phase); respiratory-triggered two-dimensional fat-suppressed axial T2-weighted turbo spin-echo (TR/TEeff 1600/80 ms); and phase); respiratory-triggered two-dimensional fat-suppressed time [TE], 292/2.3 ms at in-phase and 292/1.1 ms at opposed-phase imaging. Hepatocyte-phase images with the same three-dimensional spoiled fast field-echo sequence (except for a parallel imaging factor of 1 and acquisition of 90 slices during 22-s breath holding) imaging. Hepatocyte-phase images with the same three-dimensional spoiled fast field-echo sequence (except for a parallel imaging factor of 1 and acquisition of 90 slices during 22-s breath holding) were obtained 15–20 min (mean, 18.6 min) after an intravenous bolus injection of gadoxetic acid (Eovist or Primovist; Bayer Schering Pharma) at 0.025 mmol/kg body weight.

2.3. Quantitative image analysis

Quantitative analysis was conducted on a gadoxetic acid-enhanced hepatocyte-phase transaxial image using a prototype DICOM viewer. All measurements were performed by two radiologists in consensus (and with 5 and 13 years of post-training experience in interpreting body MR images, respectively) who had no knowledge of the clinical, hematological or radiological information regarding the patients. The hepatic contour abnormality was quantified on the right lobe at the hepatic hilar level and converted to HFI using in-house prototype software. The algorithm consisted of following several steps.

i. Extraction of hepatic contour

Gadoxetic acid-enhanced hepatocyte-phase transaxial image was converted to binary image. The hepatic contour was semi-automatically extracted using quarter pixel level plots on the arbitrary place of the right hepatic lobe at the hepatic hilar level (Fig. 1a).

ii. Calculation for the amount of characteristic

The extracted hepatic contour line was represented on the X–Y coordinate to generate hepatic profile curves (f0(t)). An approximate curve (Dn) was then determined by a least-square approach with n-th degree polynomial equation that produced the highest R2 value (Fig. 1b). Difference between the approximate curve of the hepatic profile (Dn) and (f0(t)) was calculated (Sn = Dn – f0(t)) (Fig. 1c). The 1 standard deviation (SD) of Sn was expressed as HFI in this study.

2.4. Statistical analysis

Statistical analysis was performed using commercially available software (SPSS version 17.0, SPSS Inc., Chicago, IL). The relationship between HFI and Child-Pugh score was evaluated by calculating Pearson correlation coefficient. Patient age, gender, albumin, total bilirubin, aspartate transferase (ALT) level, alanine transferase (ALT) level, percent prothrombin time, platelet count, alpha-fetoprotein (AFP), protein induced by vitamin K absence-II (PIVKA-II), and HFI were compared between patients with (n = 54) and without HCC (n = 44) using the Mann–Whitney U test and were tested as a risk factor for the development of HCC as determined by the odds ratio with logistic regression analysis. Post hoc power analyses were performed in terms of the type II error and effect size using commercially available software (G*Power, version 3.1.2, University of Duesseldorf, Germany). P values of less than 0.05 were considered significant.

3. Results

Table 1 demonstrates background characteristics of the patients with and without HCC. No significant difference was found in patient age (P = 0.34). Significant differences were found in Child-Pugh score in lower classes (P < 0.001). There was no significant difference in the ratio of Child-Pugh class C (P = 0.37) and number of the patients with the history of interferon therapy (P = 0.67). HIF was significantly correlated with Child-Pugh score (r = 0.85, P < 0.001) (Fig. 2).

Quantitative values between two groups are summarized in Table 2. We found no significant difference in serum albumin (P = 0.44), total bilirubin (P = 0.76), AST (P = 0.06), ALT (P = 0.58), platelet count (P = 0.27), and percent prothrombin time (P = 0.13). However, the HFI (P < 0.001), alpha-fetoprotein (P < 0.001), and PIVKA-II (P = 0.01) were significantly higher in patients with HCC than those without HCC.

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Fig. 1. 70-year-old man with HCC. (a) Gadoxetic acid-enhanced hepatocyte phase image obtained at hepatic hilar level was evaluated. Hepatic contour was semi-automatically profiled with 128 points of quarter pixel size at an arbitrary region using image thresholding. (b) Extracted hepatic contour was represented as hepatic profile curve \( f(x) \). An approximate curve \( D(x) \) was determined by a least-square approach with \( n \)-th degree polynomial equation which produced the highest \( R^2 \) value. (c) The difference between \( D(x) \) and \( f(x) \) was calculated \( S(x) = D(x) - f(x) \) and then standard deviation of \( S(x) \) (SD) was expresses as HFI in this study.

Boxplots for HFI in the two patient groups are shown in Fig. 3. The HFI was significantly higher in patients with HCC \((0.58 \pm 0.86)\) than those without \((0.36 \pm 0.11)\) \((P<0.001)\). Logistic analysis revealed that only HFI was a significant risk factor for HCC, with an odds ratio (95% confidence interval) of 26.4 (9.0–77.8) using a cutoff value of 0.395. Post hoc power analysis showed that we had 79% power to detect a 5% difference between the patients with and without HCC.

4. Discussion

Previously reported risk factors for HCC development include advanced age, male gender, alcohol abuse, lower platelet count, high serum AFP level, low serum albumin level, high serum ALT level, and cirrhosis \([13,14]\). Among these risk factors, several studies have shown that the risk of HCC development in patients with chronic hepatitis C is higher in those with cirrhosis than in those with chronic hepatitis, although risk appears to vary geographically \([15,16]\). According to a large-scale study involving 490 untreated and 2400 interferon-treated patients with chronic hepatitis C, the annual incidence of HCC increased with the degree of liver fibrosis: untreated patients with stage F0 or F1 fibrosis had a 0.5% incidence that increased to 7.9% for patients with stage F4 fibrosis (cirrhosis); and interferon-treated patients with stage F0 or F1 fibrosis had a
0.08% incidence that increased to 4.2% for patients with stage F4 fibrosis [17].

Morphologic changes of the liver associated with cirrhosis include atrophy of the quadrate and the right lobe as well as hypertrophy of the left lateral segment and the caudate lobe [18]. Several reports [19–21] have proposed that a disproportionate decrease in the portal blood flow or differences in the concentrations of various hormones, hepatotrophic factors, and nutrients in the regional portal blood can contribute to the morphologic changes of the cirrhotic liver. At ultrasonographic scanning, liver surface nodularity reflects the presence of the regenerative nodules and fibrous septa that are the essential histologic findings for the diagnosis of cirrhosis [10,22]. Colli et al. [10,22] investigated the accuracy of various ultrasonographic signs to assess the degree of liver fibrosis, including surface nodularity and caudate lobe hypertrophy. Among these signs, the presence of hepatic surface nodularity revealed the highest diagnostic accuracy, with 95% specificity. Furthermore, a recent study using a computer-aided quantification and analysis reported that the hepatic surface nodularity on gadoxetic acid-enhanced MR images achieved a highly accurate diagnosis of hepatic fibrosis at stages F3 and F4 [12]. In our study, though we did not include the histopathological fibrosis information, HFI showed significant strong correlation with Child-Pugh score.

Recent studies have shown that gadoxetic acid-enhanced MR imaging readily detects early-stage HCCs [23,24]. Although qualitative, the detected imaging features were analyzed and applied to accurately diagnose HCCs. Our study presents the new perspective that some of the detected imaging features can be quantitatively analyzed and used not only for the diagnosis of HCCs, but also as biomarkers for HCC development. We demonstrated that HFI quantified on the basis of hepatic contour abnormality served as an independent, significant risk factor for HCC development as well as a potential biomarker for selecting patients at high risk for developing HCC, using routine gadoxetic acid-enhanced MR imaging. If indeed HFI identifies patients at high risk for HCC, then it could form the basis of a rationale surveillance for patients with chronic hepatitis C.

The quantification of HFI was performed on the gadoxetic acid-enhanced hepatocyte-phase transaxial images acquired using the three-dimensional spoiled fast field-echo sequence. The high contrast resolution with the fat-suppressed three-dimensional gradient-echo imaging of the liver facilitated the acquisition of thin-section images, increased the spatial resolution, and improved the accuracy in the extraction of hepatic contours. The gadoxetic acid contrast medium injected intravenously is gradually taken up by hepatocytes and eventually excreted via the biliary pathway. Peak liver signal intensity is noted 20 min after the injection, followed by a plateau-like enhancement of about 2 h duration [25]. Compared to MR imaging, contrast-enhanced CT images obtained during the portal venous phase also demonstrate excellent contrast of hepatic parenchyma [26,27]. We initially attempted to use CT images for the computer-aided hepatic contour analysis. However, in our implementation, we did not have success with CT images, largely because the contours of the liver were not sufficiently distinctive from the adjacent chest walls or hemidiaphragm on CT images.

There seems to be a strong relationship between the hepatic contour abnormality, the hepatic fibrosis stages [12] and HCC development. However, a variety of other hepatic pathologies may cause hepatic contour abnormality: Lipson et al. [28] report that hepatic contour abnormalities are often seen on CT or MR imaging, and that intrinsic disorders of the liver that might cause contour abnormalities consist of hepatic tumors, cirrhosis and confluent hepatic fibrosis, infarction and vascular occlusion, treatment change, and perihepatic diseases. Further study is necessary to assess the relationship between HFI and the other disease conditions that possibly cause hepatic contour abnormalities.

Our study has several limitations. First, this is a single-institution study using a single MR system. Likewise, this study had a relatively small sample size and study period. Although we demonstrated a very high odds ratio for the risk of HCC, a multi-center trial and longitudinal observation of a large population is required to confirm the generalizability of our finding. Second, we used a single slice image to generate the HFI in this study. Quantification of whole liver contour abnormality would be requested for the next trial. Third, we did not include other etiologies causing chronic hepatitis, such as type B hepatitis, alcohol abuse, or nonalcoholic steatohepatitis. Again, an additional study with a more diverse cohort is warranted to investigate the degree of other pathologies affecting hepatic morphological abnormalities.

In conclusion, we determined that the computer-generated, hepatic morphological index expressed as HFI was highly predictive for the development of HCC in patients with chronic hepatitis C. This index may serve as an important imaging biomarker for clinical management of these patients.

## Conflicts of interest

We have no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

## Acknowledgment

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