liver (HR 9.41; 95% CI, 3.47–25.46: $p < 0.001$) were the only independent risk factors for HCC development (Table 2).

We further assessed the effect of a non-clean liver on the risk of HCC development in subgroups of these patients (Fig. 4). We found that belonging to the non-clean liver group was a significant risk factor in patients without HBV. Notably, this designation was particularly valuable for patients who are generally regarded as at low risk for HCC development: those without cirrhosis (HR 37.23; 95% CI, 3.30–419.71: $p = 0.003$) and those with high platelet counts (HR 33.42; 95% CI, 6.69–166.94: $p < 0.001$).

DISCUSSION

This study revealed presence of hypovascular hypointense liver nodules (non-clean liver) on gadoxetic acid-enhanced MRI, is a significant risk factor for subsequent development of typical HCC not only at the same sites but also at the different sites from the initial nodules. The incidence of development of typical HCC in the non-clean liver patients was >50% during a 3-year follow-up period, indicating these higher-risk patients should be rigorously investigated for the early detection of HCC during follow-up.

In the present study, 6 of the 18 patients in the non-clean liver group developed typical HCCs at the same site of the initial nodules during the subsequent 3 years (11.1%/year). Most of the hypovascular hypointense nodules on gadoxetic acid–enhanced MRI are considered precursor lesions of typical HCCs, such as early HCCs or high-grade dysplastic nodules, on histological examination (13-15), while it has been reported that most hypovascular nodules exhibiting high- to iso-intensity signals in the hepatocyte phase are benign hepatic nodules (14, 15). Recent studies have suggested that a reduction of OATP 1B3 (OATP 8) transporter expression begins at the earliest stage of hepatocarcinogenesis (21, 22), before changes in vascularity such as decreased portal flow or increased arterial flow. The progression rate of the small hypovascular hypointense nodules to typical HCC was reported as 10-17% / year (9, 10), which is comparable to the present study. Typical HCCs arose exclusively among the nodules ≥8 mm, as in previous studies that the larger size of the hypovascular hypointense nodules is the risk factor for progression to typical HCCs in the initial MRI study (9, 10).

Hyperintensity on T2WIs (12) or diffusion-weighted images (DWIs) (11) also was reported to be useful for prediction of typical HCC progress in hypovascular hypointense nodules. In our patients, none of the nodules in the non-clean liver group showed hyperintensity on T2WIs, suggesting that the hepatocyte phase is more sensitive for detecting the early-stage of hepatocarcinogenesis (15). DWIs were not evaluated in this study because this usually detects pathologically advanced HCCs of larger size or with hypervascularity (23). Thus, it is reasonable that the hepatocyte phase can effectively recognize the earliest stage of HCC development without T2WIs or DWIs.

In 11 of 17 patients, typical HCCs developed at sites other than the initially detected hypovascular hypointense nodules. As shown in Figure 3, the incidence rates of such HCCs in the non-clean liver group was significantly higher than in the clean liver group ($p = 0.003$), indicating a non-clean liver itself is a risk factor for HCC development, apart from the detectable hypovascular hypointense nodules. In addition, 4 patients with nodules even below 8mm, 2 patients developed HCC at different sites from the initial nodules during follow up (data not shown). Taken together, a liver with non-clean liver has the higher potential for hepatocarcinogenesis or for undetectable precursor lesions. The non-clean liver might reflect more advanced genetic or epigenetic changes in the background hepatocytes, however, the detailed biological mechanism is not clear in this study.

Non-clean liver was an independent risk factor for the development of typical HCC, apart from well-documented risk factors (Table 2), such as cirrhosis (24), ALT (25), γ-GTP (26), age and AFP (27). A non-clean liver is a significant risk for HCC development also for those without cirrhosis or with high platelet counts (Figure 4). This means patients at more increased risk of HCC development can be discerned as a

non-clean liver even among low-risk subgroups.

Conversely, patients without such nodules (clean liver group) showed a significantly lower risk of developing typical HCC than those with non-clean livers (0.0% vs. 11.1% in 1-year, 6.8% vs. 55.5% at 3-years follow-up; $p < 0.001$), suggesting that gadoxetic acid-enhanced MRI could detect precursor lesions sensitively enough to rule out immediate (within 1 year) development of typical HCC. Although 7 patients in the clean liver group developed typical HCCs only after 1 year, these patients had other risk factors for HCC development, including lower platelet counts, implying more advanced liver cirrhosis, or high AFP (data not shown). Such HCCs might arise from precursor lesions that cannot be visualized by current imaging techniques.

This study is a retrospective study and has some limitations. We included patients with HBV and HCV together, because gadoxetic acid-enhanced MRI findings or HCC development do not differ between these two groups and HBV or HCV infection is not an independent risk factor for typical HCC development. However, the number of HBV patients was too small ($n = 26$) to statistically confirm the current result when limited to HBV patients only. Prospective studies with larger numbers of patients who have uniform liver disease etiologies and imaging intervals are needed to verify our findings in different settings. Although the imaging interval of the non-clean liver group was shorter than the clean liver group (3 vs. 4 months: $p = 0.015$), the median intervals between the initial MRI and HCC diagnosis was 16 months in the non-clean liver group and 21 months in the clean liver group. They are short enough for cumulative detection of HCC development for three years and it is assumed that there was little influence on the conclusions.

In conclusion, patients with chronic viral liver disease are at high risk for

developing typical HCCs at any sites of the liver if they have hypovascular hypointense nodules on gadoxetic acid-enhanced MRI. These patients should be closely followed up for developing typical HCC not only at the same site but also at the different sites from the initial nodule.

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FIGURE LEGENDS

Figure 1. Patient inclusion criteria. "*De novo* HCC" is a typical HCC that developed at sites in which no nodules had been seen on the initial gadoxetic acid-enhanced MRI.

Figure 2. Cumulative incidence rates of typical HCC development in the non-clean and clean liver groups.

Figure 3. Cumulative incidence rates of typical HCC at sites in which no nodules had been seen on the initial gadoxetic acid-enhanced MRI, *i.e.* "*de novo* HCC".

Figure 4. Stratified analyses of the non-clean liver as a risk factor for typical HCC development.

Table 1. Baseline patient characteristics.

Characteristics	Total n = 127	Non-clean liver n = 18	Clean liver n = 109	p value
Age in years	65 (30-88)	68 (46-82)	64 (30-88)	0.15
Male/female	68/59	10/8	58/51	1.00
Non-cirrhosis/cirrhosis	59/68	6/12	53/56	0.31
HBV/HCV	26/101	5/13	21/88	0.53
Platelet count ($\mathbf{x}10^9$/L)	122 (30-410)	102 (46-187)	125 (30-410)	0.07
ALT (IU/L)	32 (7-206)	32 (14-95)	32 (7-206)	0.97
γ-GTP (IU/L)	31 (9-305)	31 (13-258)	31 (9-305)	0.68
AFP (ng/mL)	4 (1-582)	8 (2-181)	4 (1-582)	0.19

Note: Continuous data are shown as medians (range).

Table 2. Variables that predict HCC development: univariate and multivariate analyses.

	Univariate		Multivariate	
Variables	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Male	0.56 (0.29-1.95)	0.755		
Age (per year)	1.06 (1.00-1.12)	0.039	1.08 (1.01-1.16)	0.024
Cirrhosis	14.37 (1.90-108.44)	0.009	3.54 (0.37-33.77)	0.231
HCV (vs. HBV)	4.39 (0.58-33.17)	0.151		
Platelet count (per 10^{10}/L)	1.19 (1.06-1.33)	0.003	1.17 (1.03-1.35)	0.017
ALT (per IU/L)	1.00 (0.99-1.02)	0.423		
γ-GTP (per IU/L)	1.00 (0.99-1.01)	0.688		
AFP > 10 ng/mL	3.98 (1.47-10.77)	0.006	1.47 (0.49-4.33)	0.486
Non-clean liver	12.36 (4.68-32.61)	< 0.001	9.41 (3.47-25.46)	< 0.001

Fig. 1

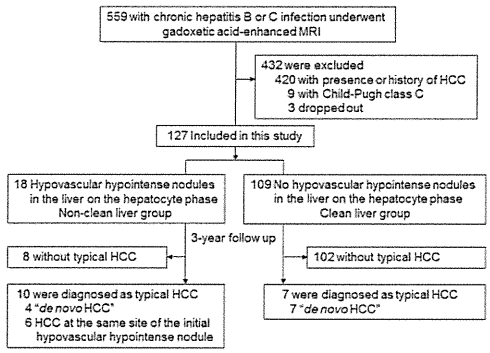

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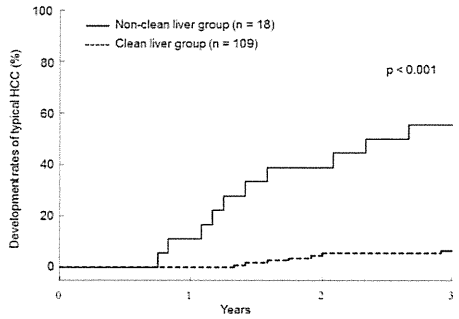
Fig. 2

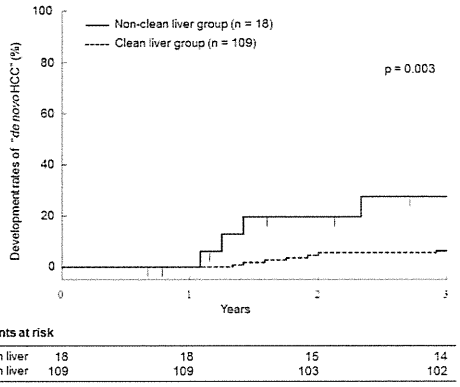


No. of patients at risk

Non-Clean liver	18	16	11	8
Clean liver	109	109	103	102

hepr_12309_f2

Fig. 3

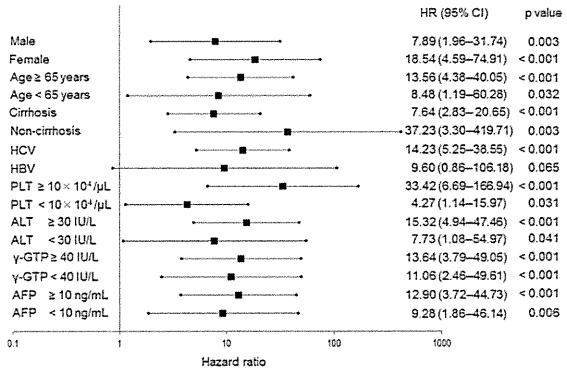


No. of patients at risk

Non-Clean liver	18	18	15	14
Clean liver	109	109	103	102

hepr_12309_f3

Fig. 4



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Original Research

Presence of a Hypovascular Hepatic Nodule Showing Hypointensity on Hepatocyte-Phase Image Is a Risk Factor for Hypervascular Hepatocellular Carcinoma

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Purpose: To determine whether the presence of a hypovascular nodule in the liver showing hypointensity on hepatocyte-phase of gadoxetic acid-enhanced magnetic resonance imaging (EOB-MRI) is a risk factor for hypervascular hepatocellular carcinoma (HCC) in patients with chronic liver disease.

Materials and Methods: Forty-one patients with pathologically confirmed hypervascular HCC and 41 age- and gender-matched controls were retrospectively selected. These patients had undergone EOB-MRI at least twice: the latest EOB-MRI and EOB-MRI performed more than 6 months earlier. History of hypervascular HCC, presence of a hypointense hypovascular nodule in previous hepatocyte-phase MR images, percent prothrombin time, platelet count, serum levels of albumin, total bilirubin, aspartate aminotransferase, alanine aminotransferase, α-fetoprotein, and protein induced by vitamin K absence-II (PIVKA-II) were variables evaluated by multivariate logistic regression analysis.

Results: Multivariate analysis revealed that serum albumin level (odds ratio [95% confidence interval], 0.19 [0.06–0.57]; $P = 0.0024$), history of hypervascular HCC (8.62 [2.71–32.8]; $P = 0.0001$), and presence of a hypointense hypovascular nodule (4.18 [1.18–17.2]; $P = 0.0256$) were significant risk factors for hypervascular HCC.

Conclusion: Patients with chronic liver disease showing a hypointense hypovascular nodule in the liver on hepatocyte-phase EOB-MRI have a high risk of HCC development.

Key Words: magnetic resonance imaging; gadoxetic acid; hepatocyte phase; hepatocellular carcinoma; risk factors
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IN THE CIRRHOTIC LIVER, hepatocellular carcinoma (HCC) develops by multistep hepatocarcinogenesis from a dysplastic nodule, through early HCC, to advanced HCC (1). The 5-year survival rate is higher among patients with early HCC than among those with advanced HCC. Therefore, risk assessment of HCC is essential for managing patients with chronic liver disease.

Early HCC may be detected as a hypointense hypovascular nodule in the cirrhotic liver by hepatocyte-phase gadoxetic acid-enhanced magnetic resonance imaging (EOB-MRI) (2). Recent studies have revealed a high incidence of hypervascularization in nonhypervascular nodules showing hypointensity in earlier hepatocyte-phase EOB-MR images (3–5). Such hypervascularization indicates the possibility of hypervascular HCC development. However, patients with these nodules frequently develop HCC in parts of the liver where no nodule was previously observed by EOB-MRI. Therefore, we hypothesized that patients with hypointense hypovascular nodules in the liver observed by hepatocyte-phase EOB-MRI might have a high risk of HCC development and could develop hypervascular HCC not only from the hypovascular nodules but also from any part of the liver.

To validate this hypothesis, we investigated whether the presence of a hypovascular nodule showing hypointensity on hepatocyte-phase EOB-MRI is a risk factor for hypervascular HCC in patients with chronic liver disease.

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Table 1
Patient Demographic Data

Parameter	With HCC	Without HCC	P
Number of patients	41	41	
Mean age (SD)	70.1 (7.29)	70.0 (7.28)	
Men:women	26:15	26:15	
Interval [days] (SD)	337 (202)	333 (143)	0.4896
Liver disease			0.4313
Viral hepatitis type C	29	28	
Viral hepatitis type B	5	5	
Alcoholic	4	1	
Other	3	7	

Interval means the duration between the previous MRI and current MRI.
Interval was compared by Mann-Whitney *U*-test and liver disease was compared by the χ^2 test.

MATERIALS AND METHODS

Subjects

This retrospective case–control study was performed in accordance with the principles of the Declaration of Helsinki. The institutional Ethics Committee approved the study protocol and waived the need for written informed consent from the subjects.

First, a radiologist with 8 years of experience reviewed the records of MR examinations performed at our institute from January 2008 to April 2012 to identify patients with chronic liver disease who had undergone EOB-MRI. If more than one EOB-MRI was performed per patient, the latest examination was considered current MRI. EOB-MRI for staging or screening of liver cancer over 6 months earlier was considered previous MRI. From the records of patients who had undergone both previous and current MRI ($n = 746$), the radiologist selected the current MRI reports that suggested hypervascular HCC ($n = 220$). Patients with suspected HCC on EOB-MRI but without pathological confirmation ($n = 151$) and those with other hepatic masses (metastasis, $n = 13$; cholangiocarcinoma, $n = 15$) were excluded. Finally, 41 patients (26 men and 15 women; age range, 54–85 years, mean age, 70.1 years) were included as cases (with-HCC group) in this study. HCC had been pathologically confirmed by partial hepatectomy ($n = 24$) or percutaneous needle biopsy ($n = 17$). No tumor was found in the liver of the remaining 526 patients by current MRI; 41 age- and gender-matched controls (without-HCC group) were selected from these patients (Table 1).

EOB-MRI

EOB-MRI had been performed in all patients using a superconducting magnet operating at 1.5 T (Signa EXCITE HD; GE Medical Systems, Milwaukee, WI) and an 8-channel phased-array coil. Dynamic fat-suppressed gradient-echo T1-weighted images with a 3D acquisition sequence (liver acquisition with volume acceleration) had been obtained before (precontrast) and at 20–30 seconds (arterial phase, scan timing was adjusted by using the fluoroscopic triggering technique), and 1 (portal venous phase), 2 (late phase), 5, 10, and 20 minutes (hepatocyte phase) after the administration of gadoxetic acid (EOB Primovist; Bayer HealthCare, Osaka, Japan). The contrast material (0.025 mmol/kg body weight) had been administered as an intravenous bolus at a rate of 1 mL/s via an intravenous cubital line (with 20 or 22G), which had been flushed with 20 mL saline using a power injector (Sonic Shot 50; Nemoto Kyorindo, Tokyo, Japan). Hepatocyte-phase images of 20 minutes acquired in the transverse and sagittal planes were used for evaluation in this study. A section thickness of 5 mm and a 2.5 mm overlap (ie, 2.5 mm interval) were applied. The repetition time / echo time ratio was 3.8/1.9 msec; flip angle, 12°; number of signals acquired, 1; field of view, 35–42 × 40–45 cm; matrix size, 320 × 192; acquisition time, 18 seconds; and parallel imaging (ASSET) factor, 1.75.

Statistical Analyses

The following variables were analyzed as potential risk factors of HCC development: serum albumin, total bilirubin, aspartate aminotransferase, alanine aminotransferase (ALT), α-fetoprotein, and protein induced by vitamin K absence-II levels; percent prothrombin time and platelet count; history of hypervascular

Table 2
Results of the Univariate Analysis

Parameter	With HCC	Without HCC	P
Albumin (g/dL)	3.7 (3.7, 2.7–4.8)	4.0 (4.0, 2.9–4.9)	0.0176
Total bilirubin (mg/dL)	0.8 (0.7, 0.3–3.2)	0.7 (0.6, 0.2–2.1)	0.4895
Aspartate aminotransferase (U/L)	50 (44, 21–146)	42 (39, 16–98)	0.1389
Alanine aminotransferase (U/L)	41 (35, 10–162)	38 (29, 9–117)	0.3857
Percent prothrombin time (%)	75.1 (71.7, 51.4–104)	80.4 (78.9, 53.5–119.9)	0.0591
Platelet count (10^9/L)	117 (97, 48–377)	137 (128, 52–356)	0.1957
α-Fetoprotein (ng/mL)	46.3 (10.4, 1.8–640)	17.3 (4.3, 0.9–256)	0.0001
Protein induced by vitamin K absence-II (mAU/mL)	397 (17, 4–15135)	29 (17, 9–338)	0.5578
History of hypervascular HCC	31/41 (75.6%)	16/41 (39.0%)	0.0008
Presence of hypointense hypovascular nodule in hepatocyte-phase EOB-MR images	15/41 (36.6%)	5/41 (12.2%)	0.0101

Serum marker levels were analyzed by the Mann–Whitney *U*-test and are expressed as means (median, range). Categorical variables were analyzed by the χ^2 test and are represented as n/N (%).

Table 3
Results of the Multivariate Analysis

Parameter	*P*	Odds ratio (95% confidence interval)
Age (per year)[a]	0.2544	0.96 (0.88–1.03)
Albumin (per 1.0 g/dL)	0.0024	0.19 (0.06–0.57)
α-Fetoprotein (per 1.0 ng/mL)	0.6481	1.00 (0.99–1.02)
History of hypervascular HCC	0.0001	8.62 (2.71–32.8)
Presence of hypointense hypovascular nodule in hepatocyte-phase EOB-MR images	0.0256	4.18 (1.18–17.2)

Although age-matched controls were selected, patient age was added as a variable to ensure the exclusion of an age effect.

HCC; and presence of a hypointense hypovascular nodule in hepatocyte-phase images obtained by previous MRI, which included nodules that were considered hypervascular HCC on current MRI and those that remained hypovascular on current MRI with or without increasing in size.

Categorical and continuous variables were compared using the χ^2 test and Mann–Whitney *U*-test, respectively. For multivariate analysis, the odds ratio (OR) was estimated by logistic regression analysis using age and the variables showing significant differences between the with-HCC and the without-HCC groups in the univariate analysis. Although age-matched controls were selected, patient age was added as a variable to ensure the exclusion of an age effect for enhancing the adjustment of age between the groups. Data analysis was performed by using JMP software v. 10 (SAS Institute Japan, Tokyo, Japan). A two-sided *P*-value of less than 0.05 was considered significant.

RESULTS

Univariate Analysis

The with-HCC and without-HCC groups showed significant differences in presence of a hypointense hypovascular nodule in hepatocyte-phase images obtained by previous MRI (*n*/*N* [%], 15/41 [36.6%] vs. 5/41 [12.2%]; $P = 0.0101$), serum albumin level (median [range], 3.7 [2.7–4.8] vs. 4.0 [2.9–4.9] g/dL; $P = 0.0176$), serum α-fetoprotein level (10.4 [1.8–640] vs. 4.3 [0.9–256] ng/mL; $P = 0.0001$), and history of hypervascular HCC (31/41 [75.6%] vs. 16/41 [39.0%]; $P = 0.0008$) (Table 2).

Multivariate Logistic Regression Analysis

Serum albumin level (OR [95% confidence interval], 0.19 [0.06–0.57]; $P = 0.0024$), history of hypervascular HCC (8.62 [2.71–32.8]; $P = 0.0001$), and presence of a hypointense hypovascular nodule in hepatocyte-phase images obtained by previous MRI (4.18 [1.18–17.2]; $P = 0.0256$) were significant risk factors for hypervascular HCC (Table 3, Fig. 1).

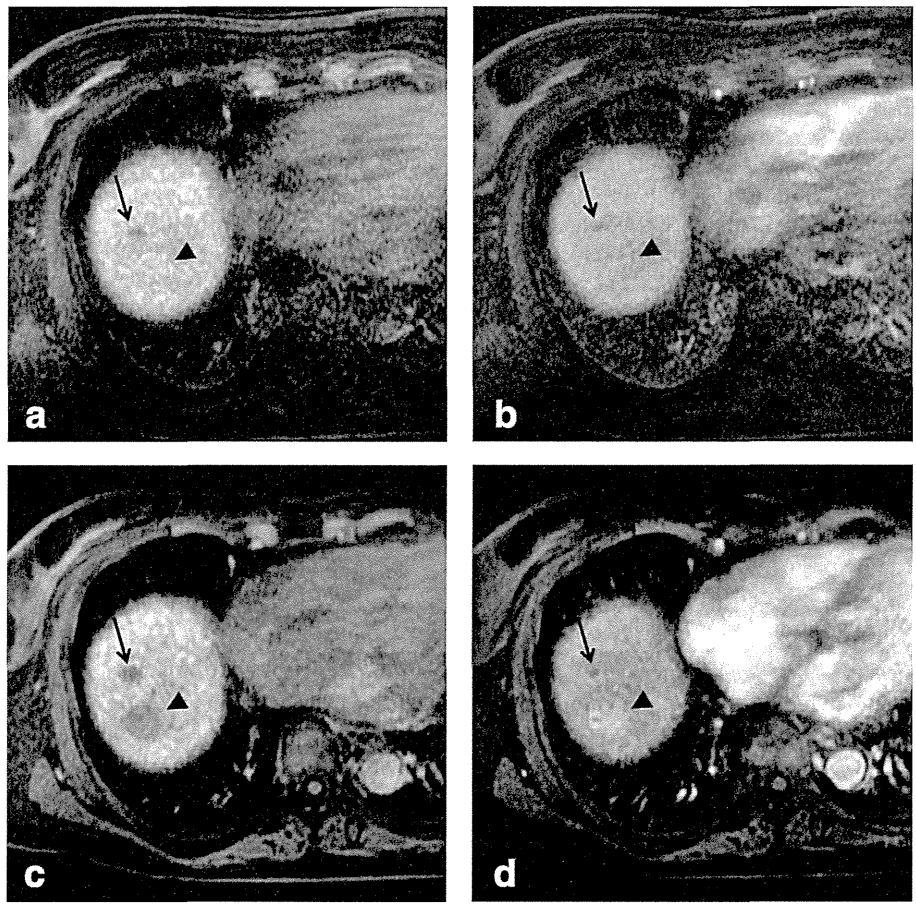

Figure 1. Findings in a 70-year-old woman with viral hepatitis type C. There was a hypointense nodule in S8 measuring 10 mm on hepatocyte-phase EOB-MR image of previous MRI (arrow). This nodule did not show hypervascularity on the arterial-phase image of previous MRI (arrow). This nodule slightly increased in size, measuring 12 mm (arrow), and another hypointense lesion measuring 20 mm is visible behind the nodule (arrowhead) of current MRI. The first nodule does not show hypervascularity on the arterial-phase image (arrow), whereas the second nodule shows hypervascularity (arrowhead) on current MRI. The second nodule could not be detected by previous MRI (arrowhead). **a:** Hepatocyte-phase EOB-MR image of previous MRI. **b:** Arterial-phase image of previous MRI. **c:** Hepatocyte-phase EOB-MR image of current MRI. **d:** Arterial-phase image of current MRI.

DISCUSSION

In this study we investigated whether the presence of a hypovascular nodule showing hypointensity on hepatocyte-phase EOB-MRI is a risk factor for hypervascular HCC in patients with chronic liver disease. The results of the multivariate analysis validate our hypothesis that patients with hypointense hypovascular nodules in the liver observed by EOB-MRI might have a high risk of HCC development. We also found that the serum albumin level and a history of hypervascular HCC are independent risk factors for hypervascular HCC. 63.4% (26/41) of the hypervascular HCCs were not found on previous MRI. If we took MRI by thinner slice (ie, 1 mm), more lesion may be detected on previous MRI. Some of cases had a long interval (ie, 1143 days, 954 days, or 678 days). Some nodules might be visible provided a shorter-interval MRI.

Recent advances in imaging techniques may enable earlier and more accurate diagnosis of HCC (6–9). Gadoxetic acid, a liver-specific contrast agent that is retained by hepatocytes and excreted into the bile ducts (10,11), allows monitoring of small lesions over a long period. Hypovascular nodules in the cirrhotic liver that are found incidentally in routine clinical MRI scans tend to show low signal intensity, indicative of poor gadoxetic acid uptake, on hepatocyte-phase EOB-MRI (3,11–13). Such nodules are now considered early HCC or high-risk lesions for developing hypervascular HCC (14). If such a lesion occurs, it will be thought that other parts of the liver are also likely to potentially develop HCC. Such a concept is well known in oral cancer as "field cancerization" (15).

The reported risk factors for HCC include older age, male gender, heavy alcohol intake, cirrhosis, low platelet count, high serum α-fetoprotein level, low serum albumin level, high serum ALT level, and poor response to locoregional treatments (16–23). Of these, patient age and gender are unanimously considered the strongest risk factors for HCC. Because the effect of the presence of a hypointense hypovascular nodule in hepatocyte-phase EOB-MR images on HCC development might be obscured by other known risk factors, including age and gender, we attempted to account for these confounding factors by using an age- and gender-matched control group.

Not only hepatologists but also radiologists should have knowledge about the risk factors for HCC, because they are expected to evaluate images that serve as a basis for patient management (eg, to recommend the frequency of imaging). Liver screening by efficient imaging would help to identify HCC in its early stages and improve the prognosis of patients with chronic liver disease (24).

Our study was mainly limited by its retrospective design and small number of patients. A prospective study with uniform subjects would be necessary to confirm the usefulness of the presence of a hypovascular hepatic nodule showing hypointensity on hepatocyte-phase EOB-MRI as a risk factor for HCC.

In conclusion, our retrospective case–control study revealed that patients with chronic liver disease showing a hypointense hypovascular nodule in the liver on hepatocyte-phase EOB-MRI have a high risk of hypervascular HCC development. EOB-MRI is a potential tool to select such patients for subsequent MR or computed tomographic examination within a short interval.

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