

1 (13-15), and more importantly, the liver with these nodules might reflect a higher
2 potential for hepato-carcinogenesis or the presence of undetectable precursor lesions in
3 other sites of the liver. Conversely, the absence of these nodules potentially identifies
4 the patients at a low risk for subsequent typical HCC development at any sites. The
5 purpose of this study was to assess the risk of subsequent typical HCC development at
6 any sites of the liver with and without hypovascular hypointense nodules on gadoxetic
7 acid-enhanced MRI.

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METHODS

3 *Ethical review*

4 The protocol of this retrospective study was approved by the ethics committee of
5 Yamanashi University Hospital, which waived the requirement for written informed
6 consent because the study was a retrospective data analysis, with appropriate
7 consideration given to patient risk, privacy, welfare, and rights.

8

9 *Patients*

10 We recruited 559 consecutive outpatients with chronic hepatitis B virus (HBV) or
11 hepatitis C virus (HCV) infection who underwent gadoxetic acid-enhanced MRI at
12 Yamanashi University Hospital between January 2008 and December 2010. The
13 exclusion criteria were as follows: 1) presence or history of typical HCC (n = 420),
14 because intrahepatic metastasis does not always develop through the usual multistep
15 hepatocarcinogenesis process, skipping the early pathological stage with
16 hypovascularity to an advanced pathological stage even when the size is small (16, 17);
17 2) Child-Pugh class C disease (n = 9), because the hepatocyte phase findings are not
18 reliable in patients with this condition because of reduced gadoxetic acid uptake in the
19 liver (18); and 3) patients who dropped out during the 3-year follow-up period (n = 3).

20 After excluding 432 patients, 127 patients were included in this retrospective
21 cohort study. They were divided into groups with hypovascular nodules determined on
22 the arterial phase and hypointensity on the hepatocyte phase (non-clean liver group; n =
23 18 patients) and without such nodules (clean liver group; n = 109 patients) as shown in
24 Figure 1. In this study, we divided cases into two groups according to the presence or

1 absence of these nodules at the baseline, even when such nodules were initially detected
2 during the follow-up period; we assigned these patients to the clean liver group.

3

4 *Follow-up and diagnosis of HCC*

5 All 127 patients were followed-up at the liver disease outpatient clinic of our
6 institution with blood tests, including those for tumor markers, and diagnostic imaging
7 modality (US, CT or MRI). The development of typical HCC that required treatment as
8 proposed by the American Association for the Study of Liver Diseases (AASLD)
9 guidelines (19) and that was diagnosed according to imaging criteria, showing arterial
10 hypervascularity and venous phase washout, or based on histological examination of
11 liver biopsies from hypovascular nodules that grew to >10 mm during follow-up.

12 Biopsies were obtained using a 21-gauge core needle. Two patients each had a liver
13 nodule >10 mm in diameter on initial MRI (12mm and 13mm), was diagnosed on the
14 basis of the biopsy as a dysplastic nodule.

15 The endpoint of this study was the development of typical HCC not only from the
16 hypovascular hypointense nodules observed initially but also from other areas without
17 these nodules (“*de novo* HCC”). Dynamic CT and/or MRI were also performed in cases
18 with hepatic nodules detected by US, liver cirrhosis, a tendency of tumor marker
19 elevation, and difficult evaluation of the liver parenchyma by US. All the 127 patients
20 were followed-up for 3 years after the initial gadoxetic acid-enhanced MRI
21 examination. When imaging modalities led to diagnosis of HCC, recognizing
22 hypervascularization by more than one experienced radiologist and other imaging
23 modalities was regarded as the time of diagnosis of HCC. When needle biopsy was
24 performed to investigate nodules, the time of diagnosis of HCC was when the

1 pathologists and physicians examined pathological tissue and diagnosed as HCC.

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3 ***MRI***

4 MRI was performed using a superconducting magnet that operated at 1.5 Tesla
5 (Sigma EXCITE HD; GE Medical Systems, Milwaukee, WI) and an 8-channel
6 phased-array coil. First, we obtained fast spoiled gradient-echo T1-weighted images
7 (T1WIs) with dual echo acquisition and respiratory-triggered fat-saturated fast
8 spin-echo T2-weighted images (T2WIs). Dynamic fat-suppressed gradient-echo T1WIs
9 were obtained using a three-dimensional (3D) acquisition sequence before (precontrast)
10 and 20-30 s, 60 s, 2 min, 5 min, 10 min, and 20 min after the administration of
11 gadoteric acid (Primovist; Bayer Schering Pharma, Berlin, Germany). This contrast
12 agent (0.025 mmol/kg body weight) was administered intravenously as a bolus at a rate
13 of 1 mL/s through an intravenous cubital line (20–22 gauge) that was flushed with 20
14 mL saline from a power injector. The delay time for the arterial phase scan was adjusted
15 according to a fluoroscopic triggering method (20). All images were acquired in the
16 transverse plane. Sagittal plane T1WIs were also obtained during the hepatocyte phase
17 at 20 min after the injection of the contrast agent.

18

19 ***Statistical analysis***

20 All continuous values are expressed as median (range). Fischer's exact probability
21 test was used for comparisons between categorical variable and the non-parametric
22 Mann-Whitney test was used to compare differences between continuous variables.
23 Baseline clinical characteristics, including blood test results, were evaluated within 1
24 month of the initial MRI. We investigated whether or not HCC development was

1 associated with age, gender, fibrosis, etiology (HBV or HCV), platelet count, serum
2 alanine aminotransferase (ALT), γ -glutamyl transpeptidase (γ -GTP), alpha-fetoprotein
3 (AFP), and the presence or absence of hypovascular hypointense nodules.
4 Cumulative HCC development was estimated according to the Kaplan-Meier
5 method and differences in the curves were tested using the log-rank test. Risk factors for
6 HCC development were determined according to the Cox proportional hazard model.
7 Subgroup analyses with a Cox proportional hazard model were applied to estimation of
8 the hazard ratio (HR) of the non-clean liver group versus clean liver group in the
9 dichotomized subgroups. All statistical analyses were performed using JMP software,
10 version 10 (SAS Institute Japan, Tokyo, Japan). A two-sided p value <0.05 was
11 considered statistically significant.

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RESULTS

3 *Characteristics of the patients and nodules*

4 A total of 127 patients were enrolled, of whom 26 had chronic HBV infections and
5 101 had HCV infections, and 68 had virus-associated cirrhosis. No statistically
6 significant differences in the initial clinical characteristics were found between the
7 non-clean liver and clean liver groups (Table 1). Thirty five hypovascular hypointense
8 nodules were found in 18 patients in the non-clean liver group (1–5 nodules per patient)
9 at baseline (data not shown). Twenty-four of these 35 nodules were detectable only on
10 the hepatocyte phase MRI and were undetectable by US, CT and non-hepatocyte phase
11 MRI. None of the 35 nodules showed high intensity on T2WIs. The median nodule
12 diameter was 8 mm (range: 4–13 mm, 33 nodules with 10mm or less, 2 nodules with 12
13 mm and 13 mm).

14

15 *HCC incidence according to initial MRI findings*

16 HCC was diagnosed in 17 patients, 10 in the non-clean liver group and 7 in the
17 clean liver group; 14 of these patients had HCV infection. Thirteen patients were
18 diagnosed according to the AASLD imaging criteria (19). Four patients were diagnosed
19 pathologically by liver biopsies that were performed, based on enlargement of the
20 nodules of >10 mm in diameter during the observation period.

21 The cumulative 1-, 2-, and 3-year HCC incidence rates were 1.5%, 10.2%, and
22 13.4%. As determined by the Kaplan-Meier method, these rates were 11.1% (95%
23 confidence interval [CI], 0.0-25.6%), 38.8% (95% CI, 16.3-61.4%), and 55.5% (95%
24 CI, 32.6-78.5%) in the non-clean liver group and 0.0% (95% CI, 0.0-2.3%), 5.5% (95%

1 CI, 0.0-9.8%), and 6.4% (95% CI, 1.8-11.0%) in the clean liver group; the former group
2 showed significantly higher rates of development of typical HCC than the latter (p
3 <0.001) as shown in Figure 2. The median imaging intervals were 3 months (3-6
4 months) in the non-clean liver group and 4 months (2-12 months) in the clean liver
5 group. The imaging interval of the non-clean liver group was shorter than clean liver
6 group (3 vs. 4 months: $p = 0.015$). The median intervals between the initial MRI and
7 HCC diagnosis was 16 months (9-32 months) in the non-clean liver group and 21
8 months (16-35 months) in the clean liver group.

9 In 11 of 17 patients with HCC development, HCCs developed at sites in which no
10 nodules had been seen on the initial gadoxetic acid-enhanced MRI, *i.e.* "de novo HCC".
11 These HCCs were found 4 in 18 patients in the non-clean liver group (3-year HCC
12 incidence rates: 22.2%, 95% CI, 4.3-51.0%) and 7 in 109 patients in the clean liver
13 group (3-year HCC incidence rates: 6.4%, 95% CI, 1.8-11.0%). The incidence rates of
14 "de novo HCC" was significantly higher in the non-clean liver group than the clean liver
15 group ($p = 0.003$, Figure 3). In the remaining 6 patients, HCCs developed at the same
16 site of the initial nodules exclusively in 18 patients of a non-clean liver group by
17 definition, and those HCCs arose among the nodules ≥ 8 mm in the initial MRI study.

18 19 ***Risk factors for HCC development***

20 Univariate analyses showed that the significant risk factors for HCC development
21 included older age ($p = 0.039$), cirrhosis ($p = 0.009$), a low platelet count ($p = 0.003$), a
22 high AFP concentration ($p = 0.006$), and a non-clean liver ($p < 0.001$). Multivariate
23 analysis with these variables revealed that older age (HR: 1.08; 95% CI, 1.01–1.16: $p =$
24 0.024), a low platelet count (HR 1.17; 95% CI, 1.03–1.35: $p = 0.017$), and a non-clean

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

3 We further assessed the effect of a non-clean liver on the risk of HCC
4 development in subgroups of these patients (Fig. 4). We found that belonging to the
5 non-clean liver group was a significant risk factor in patients without HBV. Notably,
6 this designation was particularly valuable for patients who are generally regarded as at
7 low risk for HCC development: those without cirrhosis (HR 37.23; 95% CI,
8 3.30–419.71: $p = 0.003$) and those with high platelet counts (HR 33.42; 95% CI,
9 6.69–166.94: $p < 0.001$).

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DISCUSSION

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

10 In the present study, 6 of the 18 patients in the non-clean liver group developed
11 typical HCCs at the same site of the initial nodules during the subsequent 3 years
12 (11.1%/year). Most of the hypovascular hypointense nodules on gadoxetic
13 acid-enhanced MRI are considered precursor lesions of typical HCCs, such as early
14 HCCs or high-grade dysplastic nodules, on histological examination (13-15), while it
15 has been reported that most hypovascular nodules exhibiting high- to iso-intensity
16 signals in the hepatocyte phase are benign hepatic nodules (14, 15). Recent studies have
17 suggested that a reduction of OATP 1B3 (OATP 8) transporter expression begins at the
18 earliest stage of hepatocarcinogenesis (21, 22), before changes in vascularity such as
19 decreased portal flow or increased arterial flow. The progression rate of the small
20 hypovascular hypointense nodules to typical HCC was reported as 10-17% / year (9,
21 10), which is comparable to the present study. Typical HCCs arose exclusively among
22 the nodules ≥ 8 mm, as in previous studies that the larger size of the hypovascular
23 hypointense nodules is the risk factor for progression to typical HCCs in the initial MRI
24 study (9, 10).

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

9 In 11 of 17 patients, typical HCCs developed at sites other than the initially
10 detected hypovascular hypointense nodules. As shown in Figure 3, the incidence rates
11 of such HCCs in the non-clean liver group was significantly higher than in the clean
12 liver group ($p = 0.003$), indicating a non-clean liver itself is a risk factor for HCC
13 development, apart from the detectable hypovascular hypointense nodules. In addition,
14 4 patients with nodules even below 8mm, 2 patients developed HCC at different sites
15 from the initial nodules during follow up (data not shown). Taken together, a liver with
16 non-clean liver has the higher potential for hepatocarcinogenesis or for undetectable
17 precursor lesions. The non-clean liver might reflect more advanced genetic or epigenetic
18 changes in the background hepatocytes, however, the detailed biological mechanism is
19 not clear in this study.

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

1 non-clean liver even among low-risk subgroups.

2 Conversely, patients without such nodules (clean liver group) showed a
3 significantly lower risk of developing typical HCC than those with non-clean livers
4 (0.0% vs. 11.1% in 1-year, 6.8% vs. 55.5% at 3-years follow-up; $p < 0.001$), suggesting
5 that gadoxetic acid-enhanced MRI could detect precursor lesions sensitively enough to
6 rule out immediate (within 1 year) development of typical HCC. Although 7 patients in
7 the clean liver group developed typical HCCs only after 1 year, these patients had other
8 risk factors for HCC development, including lower platelet counts, implying more
9 advanced liver cirrhosis, or high AFP (data not shown). Such HCCs might arise from
10 precursor lesions that cannot be visualized by current imaging techniques.

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

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

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

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FIGURE LEGENDS

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

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

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

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

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1 **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 ($\times 10^9/L$)	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

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

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

Variables	Univariate		Multivariate	
	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

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