Magnetic resonance imaging-based risk factors of hepatocellular carcinoma after direct-acting antiviral therapy: A multicenter observational study

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Running title: Risk factors of HCC after DAA therapy

Conflict-of-Interest Statement

Takamichi Murakami is an Editorial Board member of Hepatology Research and a co-author of this article. To minimize bias, they were excluded from all editorial decision-making related to the acceptance of this article for publication.

This study has received funding by Bayer Yakuhin, Ltd. (Osaka, Japan). The study sponsor was not involved in any stage of the study design, data acquisition, data analysis, or manuscript preparation.

Disclosure of Ethical Statements

Approval of the research protocol: This multicenter study was approved by the institutional review boards of the seven participating centers (University of Yamanashi, Ikeda Municipal

Hospital, Kanazawa University, Kindai University, Kobe University, Gifu University, and Kagoshima University).

Informed Consent: Written informed consent was obtained from all participants.

Registry and the Registration No. of the study/trial: N/A

Animal Studies: N/A

Research involving recombinant DNA: N/A

Abstract

Aim: To determine risk factors associated with hepatocellular carcinoma (HCC) development following direct-acting antiviral (DAA) therapy.

Methods: We enrolled patients with chronic hepatitis C who underwent DAA therapy and achieved sustained virologic response at 12 weeks between 2012 and 2018. Subsequently, patients were followed up. The primary endpoint was the development of HCC or the date of the last follow-up when the absence of HCC was confirmed. Uni- and multi-variate Cox proportional hazard models were used to identify factors contributing to HCC development, including gadoxetic acid-enhanced magnetic resonance imaging findings. The cumulative incidence rates of HCC development were calculated using the Kaplan–Meier method and differences between groups were assessed using the log-rank test.

Results: The final study cohort comprised 482 patients (median age, 70.5 years; 242 men). The median follow-up period was 36.8 months. Among 482 patients, 96 developed HCC (19.9%). The 1-, 3-, and 5-year cumulative rates of HCC development were 4.9%, 18.6%, and 30.5%, respectively. Multivariate analysis revealed that age, male sex, history of HCC, and hepatobiliary phase (HBP) hypointense nodules without arterial phase hyperenhancement (APHE) were independent risk factors significantly associated with HCC development ($P <$ 0.001–0.04). The highest risk group included patients with both a history of HCC and the presence of HBP hypointense nodules without APHE (the 1- and 3-year cumulative HCC development rates were 14.2% and 62.2%, respectively).

Conclusion: History of HCC and presence of HBP hypointense nodules without APHE were strong risk factors for HCC development following DAA therapy.

Keywords

liver; hepatitis C; hepatocellular carcinoma; magnetic resonance imaging; risk factors; arterial phase hyperenhancement; direct-acting antiviral therapy; hepatobiliary phase

Abbreviations

MRI, magnetic resonance imaging; AP, arterial phase; HBP, hepatobiliary phase; APHE, arterial phase hyperenhancement; DAA, direct-acting antiviral therapy; HCC, Hepatocellular Carcinoma

Introduction

Chronic hepatitis C virus (HCV) infection is one of the prevalent underlying etiologies of cirrhosis worldwide.[1] Hepatocellular carcinoma (HCC) is frequently associated with HCV-related cirrhosis and ranks as the third most common cause of cancer-related deaths globally, following lung and colorectal cancers.[2] Traditional treatments for HCV infection, such as interferon-based regimens, have demonstrated limited efficacy in eradicating HCV compared to direct-acting antivirals (DAAs), particularly in patients with advanced liver fibrosis, and are associated with significant adverse events.[3] Recently, interferon-free DAAs have replaced interferons as the standard treatment for HCV infection, offering improved safety profiles and higher rates of sustained virologic response (SVR). A meta-analysis revealed that DAA therapy has achieved SVR rates >95% regardless of HCV genotype.[4] While chronic HCV infection can promote hepatocarcinogenesis, and its eradication may decrease the risk of HCC, the impact of viral eradication through DAA therapy on HCC development remains contentious. Some studies have reported a decrease in HCC incidence after DAA therapy [5–8], whereas others have found no significant change.[9–12] Previous investigations have identified several risk factors associated with HCC development after DAA therapy, including older age, sex, albumin levels, γ-glutamyltranspeptidase activity, fibrosis-4 index, platelet count, total bilirubin, hyaluronic acid levels, liver stiffness, α-fetoprotein levels, history of HCC treatment , and pre-treatment fibrosis stage.[5,13–17] Recently, attention has deen drawn to hepatobiliary phase (HBP) hypointense nodules without arterial phase hyperenhancement (APHE) as potential indicators of hypervascular HCC development in patients with chronic liver disease.[18,19] HBP hypointense nodules without APHE are defined as hepatic nodules that do not exhibit hyperenhancement during the arterial phase (AP) and display low signal intensity during the HBP on gadoxetic acid-enhanced magnetic resonance imaging (MRI).[20] Several studies have suggested that these nodules may predict the development of

hypervascular HCC following DAA therapy.[21–25] However, our comprehensive literature search failed to uncover any prospective multicenter observational studies focused specifically on the presence of HBP hypointense nodules without APHE prior to DAA therapy. As numerous patients, including those at high risk of HCC, currently achieve SVR, identifying patients who are at risk of developing hypervascular HCC after DAA therapy would greatly aid in their surveillance. Thus, this study aimed to elucidate the risk factors associated with hypervascular HCC development following DAA therapy.

Materials and Methods

Patients

This multicenter study obtained approval from the institutional review boards of seven participating centers (Hospital A–G). We enrolled patients with chronic hepatitis C who received DAA treatment and achieved SVR at 12 weeks (SVR12) between March 2012 and June 2018. SVR12 was confirmed by the absence of serum HCV-ribonucleic acid 12 weeks after completing DAA therapy. Prospective follow-up of patients commenced after SVR12 was achieved, and written informed consent was obtained from all participants. Gadoxetic acid-enhanced MRI was utilized to confirm the absence of hypervascular HCC at the time of patient enrollment (within 6 months of SVR12). Subsequently, all participants attended regular follow-up appointments at the outpatient clinic of the respective participating centers for liver disease management. Blood tests, including those for tumor markers (α-fetoprotein and protein induced by vitamin K absence-II), and abdominal ultrasonography were conducted every 3–6 months, while gadoxetic acid-enhanced MRI was performed every 6 months. If tumor markers were elevated or if a new liver nodule was detected during abdominal ultrasonography, gadoxetic acid-enhanced MRI was performed to confirm or exclude a diagnosis of HCC. The following patients were excluded from the study: i) those

with hypervascular HCCs at enrollment, ii) those with inadequate follow-up MRI (e.g. without contrast or poor image quality), or iii) those who were followed up for less than six months after enrollment. The primary endpoint was the development of hypervascular HCC or the date of the last follow-up where the absence of hypervascular HCC was confirmed. The observation period was defined as the time from the date of the initial MRI at enrollment to the endpoint. Data on the following baseline characteristics were recorded upon enrollment; background information (age, sex, height, and body weight), presence of liver cirrhosis (clinically diagnosed by board-certified hepatologists in each participating center), HCV genotype, history of HCC, presence of HBP hypointense nodules without APHE in the initial MRI, and blood test results including platelet count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, total bilirubin, γ-glutamyltranspeptidase, alkaline phosphatase (ALP), lactate dehydrogenase (LDH), creatinine, prothrombin time-international normalized ratio, α-fetoprotein, and protein induced by vitamin K absence-II. The presence of hepatic encephalopathy and ascites was also assessed to determine the Child-Pugh class.

DAA therapy

DAA therapy was administered by board certified hepatologists at each participating center. The specific DAA regimens for patients with genotype 1 HCV included daclatasvir/asunaprevir for 24 weeks, sofosbuvir/ledipasvir for 12 weeks, elbasvir/grazoprevir for 12 weeks, ombitasvir/paritaprevir/ritonavir for 12 weeks, or glecaprevir/pibrentasvir for 8 or 12 weeks,. The DAA regimens for patients with genotype 2 HCV included sofosbuvir/ribavirin for 12 weeks or glecaprevir/pibrentasvir for 8 or 12 weeks.

MRI protocols

Gadoxetic acid-enhanced MRI was performed using various 1.5-T or 3-T MRI systems. The imaging protocols and sequence parameters varied depending on the participating center and are summarized in Supplemental material 1. Gadoxic acid (0.025 mmol/kg) was administered intravenously at a rate of 1–2 mL/s, followed by saline flushing using a power injector.

Image analysis

All MR images obtained at each participating center were reviewed by board-certified radiologists, who evaluated the presence of HBP hypointense nodules without APHE in the initial MRI. Cysts and hemangiomas were excluded based on T2-weighted and diffusion-weighted images (T2WI and DWI). If HBP hypointense nodules without APHE were identified, those nodules were further evaluated for high signal intensity on T2-weighted or diffusion-weighted images. Subsequently, during follow-up MRIs, hypervascular HCC development was assessed. The diagnosis of hypervascular HCC was based on the criteria outlined by the Japan Society of Hepatology, which includes i) hypervascular in AP; ii) hypointensity compared to the surrounding liver parenchyma in the portal venous, transitional, or hepatobiliary phases; and iii) exclusion of hemangioma through evaluation with T2WI and DWI.[26] The development of hypervascular HCC encompassed both imaging-based multistep hepatocarcinogenesis (i.e., HCC arising from an HBP hypointense nodule without APHE)[18] and imaging-occult hepatocarcinogenesis (i.e., HCC development in an area that was not initially identified on the baseline MRI).[19]

Statistical analysis

The distribution of all continuous variables were assessed for normality using the Shapiro-Wilk test. Univariate and multivariate Cox proportional hazard models were used to identify risk factors associated with the development of hypervascular HCC. The variables analyzed

in the models included age, sex, height, body weight, body mass index, presence of liver cirrhosis, HCV genotype 1, history of HCC, diabetes mellitus, HBP hypointense nodule without APHE, blood test results, Fibrosis-4 index, and Child-Pugh class A. The cumulative incidence rates of hypervascular HCC development were calculated using the Kaplan–Meier method, and differences between the curves of each group were assessed using the log-rank test. Receiver operating characteristics (ROC) analysis was employed to determine the optimal cut-off values for continuous variables that best predicted the risk of hypervascular HCC development. All statistical analyses were performed using JMP Pro software (version 17.1.0; SAS Institute Inc.). Statistical significance was set at $P < 0.05$.

Results

Distributions of continuous variables

The normality was not confirmed for all continuous variables ($P < 0.001$–0.001). Therefore these variables were presented as median and interquartile range.

Baseline patient demographics

A total of 538 patients were initially recruited for the study. However, 56 patients were subsequently excluded based on the predetermined exclusion criteria (Figure 1). The final study cohort comprised 482 patients (median age, 70.5 [interquartile range, 64.0–77.0] years; 242 men and 239 women). Table 1 provides an overview of the baseline demographic characteristics of the final study cohort. The mean follow-up period was 34.8 ± 13.1 months (median, 36.8 months).

Risk factors associated with hypervascular HCC development

Among the 482 patients included in the study, 96 patients developed hypervascular HCC (19.9%). Among these cases, 43.8% (42/96) were classified as multistep hepatocarcinogenesis, and 56.3% (54/96) were catergorized as imaging-occult hepatocarcinogenesis. Of these 96patients, 66 had a history of HCC, of which 45.5% (30/66) were classified multistep hepatocarcinogenesis and 54.5% (36/66) were classified as imaging-occult hepatocarcinogenesis. On the other hand, there were 30 patients without a history of HCC, of whom 40.0% (12/30) were classified as multistep hepatocarcinogenesis and 60.0% (18/30) were classified imaging-occult hepatocarcinogenesis. Thirty-two patients exhibited the emergence of HBP hypointense nodules without APHE in follow-up MRIs, 5 of which developed hypervascular HCC, all of whom were included in the 42 patients classified under multistep hepatocarcinogenesis. The 1-, 3-, and 5-year cumulative rates of hypervascular HCC development were 4.9%, 18.6%, and 30.5%, respectively (Figure 2). Table 2 presents the risk factors associated with the development of hypervascular HCC. Univariate analysis identified age, male sex, liver cirrhosis, history of HCC, HBP hypointense nodule without APHE, platelet count, AST, ALT, albumin, γ-glutamyltranspeptidase, ALP, LDH, creatinine, Fibrosis-4 index, and α-fetoprotein as factors significantly associated with hypervascular HCC development ($P < 0.001–0.04$). Multivariate analysis revealed that, age, male sex, history of HCC, and HBP hypointense nodule without APHE were independent risk factors significantly associated with hypervascular HCC development ($P < 0.001–0.04$). Following ROC analysis, age ≥ 69 years was identified as the cut-off value. The incidence rate of hypervascular HCC was significantly higher in patients with a history of HCC compared to those without a history of HCC ($P < 0.001$). The cumulative rates of hypervascular HCC development at 1-, 3-, and 5-years were 11.7%, 46.9%, and 71.9%, respectively, in patients with a history of HCC. In contrast the cumulative rates of hypervascular HCC development at 1-, 3-, and 5-years were 2.0%, 8.0%, and 9.7%,

respectively, in patients without a history of HCC (Figure 3, upper left). We conducted sub-analysis to examine factors associated with post-SVR HCC in patients with a history of HCC (Supplemental material 2). Multivariate analysis was performed on three factors: non-curative treatment history of HCC, non-surgical treatment history of HCC, and interval between DAA therapy and HCC treatment. Among these factors, only non-surgical treatment history of HCC emerged as a significant factor ($P = 0.03$). The incidence rate of hypervascular HCC was significantly higher in patients with HBP hypointense nodules without APHE compared to those without this characteristic ($P < 0.001$). The 1-, 3-, and 5-year cumulative rates of hypervascular HCC development were 10.9%, 44.2%, and 61.6%, respectively, in patients with HBP hypointense nodules without APHE. In contrast the 1-, 3-, and 5-year cumulative rates of hypervascular HCC development were 2.5%, 9.9%, and 15.9%, respectively, in patients without HBP hypointense nodules without APHE (Figure 3, upper middle). The upper right graph on Figure 3 depicts the cumulative rates of hypervascular HCC development stratified by patients with a history of HCC and HBP hypointense nodules without APHE. The highest-risk group consisted of patients with both a history of HCC and HBP hypointense nodules without APHE (Group A, n= 57). The 1- and 3-year cumulative rates of hypervascular HCC development were 14.2% and 62.2%, respectively, for patients in Group A. None of the patients from Group A reached 5 years of observation. The 1-, 3-, and 5-year cumulative rates of hypervascular HCC development were 9.7%, 35.0%, and 48.6%, respectively, in patients with a history of HCC but without HBP hypointense nodules without APHE (Group B, n= 72); 7.9%, 28.1%, and 31.7%, respectively, in patients with HBP hypointense nodules without APHE, but no history of HCC (Group C, n= 64); and 0.7%, 3.4%, and 4.7%, respectively, in patients with no history of HCC or HBP hypointense nodules without APHE (Group D, n= 289) (Figure 3, upper right).

The incidence rate of hypervascular HCC was significantly higher in patients aged ≥ 69 years compared to those aged < 69 years ($P < 0.001$). The 1-, 3-, and 5-year cumulative rates of hypervascular HCC development were 6.1%, 23.8%, and 44.7%, respectively, for patients aged ≥ 69 years, while for patients aged < 69 years the rates were 3.1%, 10.9%, and 21.7%, respectively, (Figure 3, lower left). The incidence rate of hypervascular HCC was significantly higher in male patients compared to female patients ($P < 0.001$). The 1-, 3-, and 5-year cumulative rates of hypervascular HCC development were 8.0%, 25.5%, and 37.6%, respectively, for male patients, and 2.1%, 11.6%, and 33.0%, respectively, for female patients (Figure 3, lower middle). Figure 4 presents a case of imaging-based multistep hepatocarcinogenesis, whereas Figure 5 illustrates a case of imaging-occult process of hepatocarcinogenesis.

Sub-analysis regarding HBP hypointense nodule without APHE

Among the 482 patients, 121 patients were found to have an HBP hypointense nodule without APHE in the initial MRI. Among these patients, 46 (38.0%) had an HBP hypointense nodule without APHE that exhibited hyperintensity on T2WI and/or DWI, while 75 patients (62.0%) had a nodule that showed iso- or hypointensity on both T2WI and DWI. Of these 46 patients, 26.1% (12/46) demonstrated multistep hepatocarcinogenesis and 34.8% (16/46) demonstrated imaging-occult hepatocarcinogenesis. The incidence rate of hypervascular HCC was significantly higher among the patients with an HBP hypointense nodule without APHE that showed hyperintensity on T2WI and/or DWI compared to those with the nodule showing iso- or hypointensity on both T2WI and DWI ($P = 0.007$). The 1-, 3-, and 5-year cumulative rates of hypervascular HCC development were 21.7%, 57.4%, and 85.8%, respectively, in patients with HBP hypointense nodules without APHE exhibiting hyperintensity on T2WI and/or DWI. In contrast, the 1-, 3-, and 5-year cumulative rates of

hypervascular HCC development were 5.4%, 38.0%, and 54.8%, respectively, in patients with nodules showing iso- or hypointensity on both T2WI and DWI (Figure 6).

Discussion

In this study, we found that a history of HCC and the presence of HBP hypointense nodules without APHE are strong risk factors for the development of hypervascular HCC following DAA therapy, which is consistent with previous research.[21] Other studies have also demonstrated the association between HBP hypointense nodules without APHE and the development of hypervascular HCC.[22–25] According to radiological-pathological correlations, HBP hypointense nodules without APHE are considered precursors to hypervascular HCC.[27,28] In a multicenter study conducted in South Korea, HBP hypointense nodules without APHE were pathologically diagnosed as progressed and early HCCs, high-grade and low-grade dysplastic nodules, or regenerative nodules.[29] In our study, the specific diagnosis of HBP hypointense nodules without APHE was not crucial; rather, the presence or absence of these nodules was important. Although the size of HBP hypointense nodules without APHE was not examined in this study, previous research has reported that nodule size does not influence the development of hypervascular HCC.[23] The presence of such nodules may serve as a potential indicator for hypervascular HCC development in other regions of the liver.[30] The incidence rate of hypervascular HCC in patients with HBP hypointense nodules without APHE was similar to that observed in previous reports prior to the advent of DAA therapy.[18,31] Livers harboring such nodules may exhibit a predisposition to hepatocarcinogenesis in other areas of the liver. This concept may also explain why a history of HCC is a risk factor for hypervascular HCC development. Consistent with the findings of our study, patients with both a history of HCC and HBP hypointense nodules without APHE displayed a high risk of hypervascular HCC development after DAA therapy, while those

without both factors had a very low risk. The risk for patients with either a history of HCC or HBP hypointense nodules without APHE was intermediate, suggesting the possibility of risk stratification by considering both the history of HCC and the presence of HBP hypointense nodules without APHE. Surprisingly, among 96 patients who developed hypervascular HCC in this study, 56.3% (54/96) were catergorized as imaging-occult hepatocarcinogenesis, i.e., direct emergence of hypervascular HCC not through HBP hypointense nodules without APHE. Moreover, 60.0% (18/30) of post-SVR HCC emerged as imaging-occult hepatocarcinogenesis, even patients without a history of HCC before DAA therapy. Previous reports have reported the rate of imaging-occult hepatocarcinogenesis was 13.4-38.9%,[22,23,32] and the results of this study showed a higher rate than previous reports. Based on the results of this study, the liver with HBP hypointense nodules without APHE has high likelihood of having a minute hypervascular HCC undetectable by imaging. This point is clinically important, because it may influence the surveillance strategy of HCC in patients who achieved SVR.

A notable strength of this study is the sub-analysis conducted regarding HBP hypointense nodules without APHE. The incidence rate of hypervascular HCC was significantly higher in patients with HBP hypointense nodules without APHE that exhibited hyperintensity on T2WI and/or DWI, compared to patients with nodules showing iso- or hypointensity on both T2WI and DWI. Recent meta-analyses investigating risk factors for the hypervascularization of HBP hypointense nodules without APHE have reported that T2 hyperintensity and restricted diffusion are associated with an increased risk of hypervascularization in patients with HCC.[33] It is clinically important to note that our study demonstrated similar results in patients treated with DAAs, emphasizing the need for closer follow-up of patients with HBP hypointense nodule without APHE that show hyperintensity on T2WI and/or DWI.

Age and male sex were identified as independent risk factors associated with the development of hypervascular HCC [13,15–17], which is consistent with previous reports. Other factors, including γ-glutamyltranspeptidase, platelet count, total bilirubin, and α-fetoprotein, were also found to be independent risk factors, although their associations with hypervascular HCC development have shown inconsistencies in previous studies.[5,13–15,17] Notably, α-fetoprotein did not emerge as a significant risk factor for the hypervascularization of HBP hypointense nodules without APHE in a recent meta-analysis involving patients with HCC.[33] Other discrepancies could be attributed to differences in the study population, including the inclusion or exclusion of patients with a history of HCC or varying degrees of fibrosis.

This study has several limitations. First, certain parameters (e.g., hyaluronic acid and liver stiffness) reported as risk factors for hypervascular HCC development after DAA therapy in other studies were not assessed in this study. These parameters are not routinely examined in every hospital, and therefore, were not included in this analysis. Second, the diagnosis of hypervascular HCC development was based on criteria provided by the Japan Society of Hepatology; however, no cases had pathological confirmation of HCC. This limitation is inherent to image based research in the context of HCC, as biopsies are not routinely performed.

In summary, a history of HCC and the presence of HBP hypointense nodules without APHE were identified as strong risk factors for the development of HCC after DAA therapy. While the natural progression of HCC development in patients achieving SVR is still being studied, individuals with a history of HCC or HBP hypointense nodules without APHE should receive more diligent follow-up and monitoring.

Acknowledgments

We are grateful to Dr. Minoru Sakamoto (Deceased 13 August 2018) for collaboration on the early stages of this work.

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Figure legends

Figure 1: Flowchart of patient enrollment

MRI, magnetic resonance imaging

Figure 2: Cumulative rates of hypervascular HCC development among all study cohort

The 1-, 3-, and 5-year cumulative rates of hypervascular HCC development were 4.9%, 18.6%, and 30.5%, respectively.

MRI, magnetic resonance imaging

Figure 3: Cumulative rates of hypervascular HCC development according to the history of HCC, HBP hypointense nodules without APHE, stratified by patients with a history of HCC and HBP hypointense nodules without APHE, age, and sex.

The incidence rate of hypervascular HCC was significantly higher in patients with a history of HCC comapred to those without a history of HCC ($P < 0.001$) (Upper left).

The incidence rate of hypervascular HCC was significantly higher in patients with HBP hypointense nodules without APHE compared to those without HBP hypointense nodules without APHE ($P < 0.001$) (Upper middle).

Upper right graph shows cumulative hypervascular HCC development stratified by patients with a history of HCC and HBP hypointense nodules without APHE. The highest risk group was patients with both a history of HCC and HBP hypointense nodules without APHE (Group A) ($P < 0.001$).

The incidence rate of hypervascular HCC was significantly higher in patients aged ≥ 69 years comapred to those aged < 69 years ($P < 0.001$) (Lower left).

The incidence rate of hypervascular HCC was significantly higher in male than in female patients ($P < 0.001$) (Lower middle).

HCC, hepatocellular carcinoma; HBP, hepatobiliary phase; APHE, arterial phase hyperenhancement

Figure 4: A typical case of imaging-based multistep hepatocarcinogenesis.
A 72-year-old man presented with a HBP hypointense nodule without arterial phase hyperenhancement (12 mm in diameter, dotted circle and solid arrow) in segment 8 of the liver on baseline MRI. The size of this nodule did not change; however, it showed hypervascularity on the follow-up MRI performed six months after the baseline MRI. The patient had a medical history of radiofrequency ablation and transcatheter arterial chemoembolization for hepatocellular carcinoma.
MRI, magnetic resonance imaging; HBP, hepatobiliary phase

Figure 5: A typical case of imaging-occult process of hepatocarcinogenesis.
A 54-year-old man presented with a HBP hypointense nodule without arterial phase hyperenhancement (8 mm in diameter, dotted circle and solid arrow) in segment 6 of the liver on baseline MRI. In the follow-up MRI performed six months later, the nodule had slightly increased in size, measuring 10 mm; however, it still did not demonstrate hypervascularity on AP (dotted circle and solid arrow). Another hypointense nodule measuring 8 mm was visible in segment 2 of the liver, and this nodule did show hypervascularity (arrowhead). This nodule was not detectable in the baseline MRI (dotted circle). The patient had a medical history of hepatectomy, radiofrequency ablation, and transcatheter arterial chemoembolization for hepatocellular carcinoma.
MRI, magnetic resonance imaging; AP, arterial phase; HBP, hepatobiliary phase

Figure 6: Cumulative rates of hypervascular HCC development according to the signal pattern of HBP hypointense nodules without APHE.

The incidence rate of hypervascular HCC was significantly higher in patients with HBP hypointense nodules without APHE that showed hyperintensity on T2WI and/or DWI compared to those with HBP hypointense nodule without APHE that exhibited iso- or hypointensity on both T2WI and DWI ($P = 0.007$).

APHE, arterial phase hyperenhancement; HBP, hepatobiliary phase; HCC, hepatocellular carcinoma; T2WI, T2-weighted image; DWI, diffusion-weighted image

Figure 1

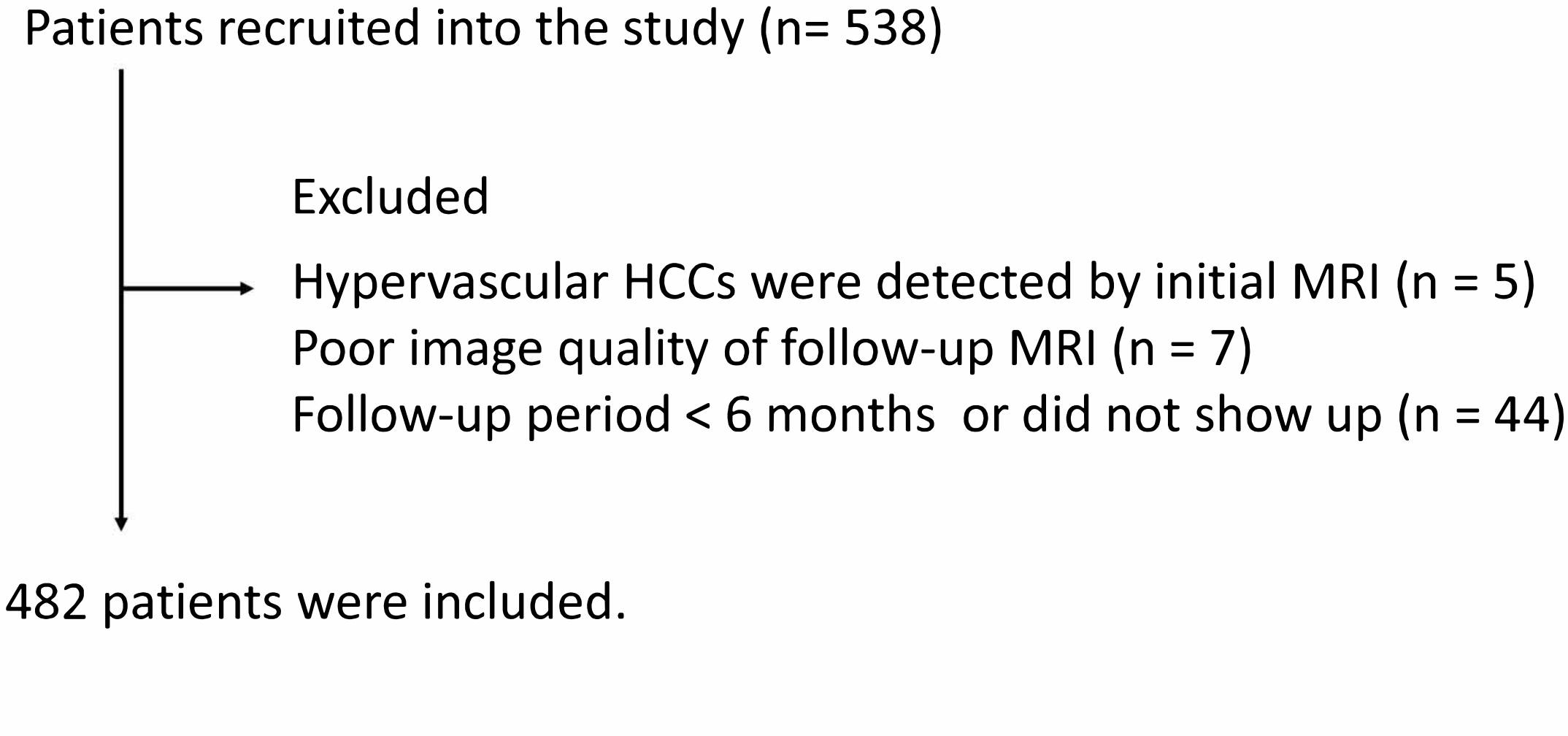

Patients recruited into the study (n= 538)
Excluded
Hypervascular HCCs were detected by initial MRI (n = 5)
Poor image quality of follow-up MRI (n = 7)
Follow-up period < 6 months or did not show up (n = 44)
482 patients were included.

Figure 2

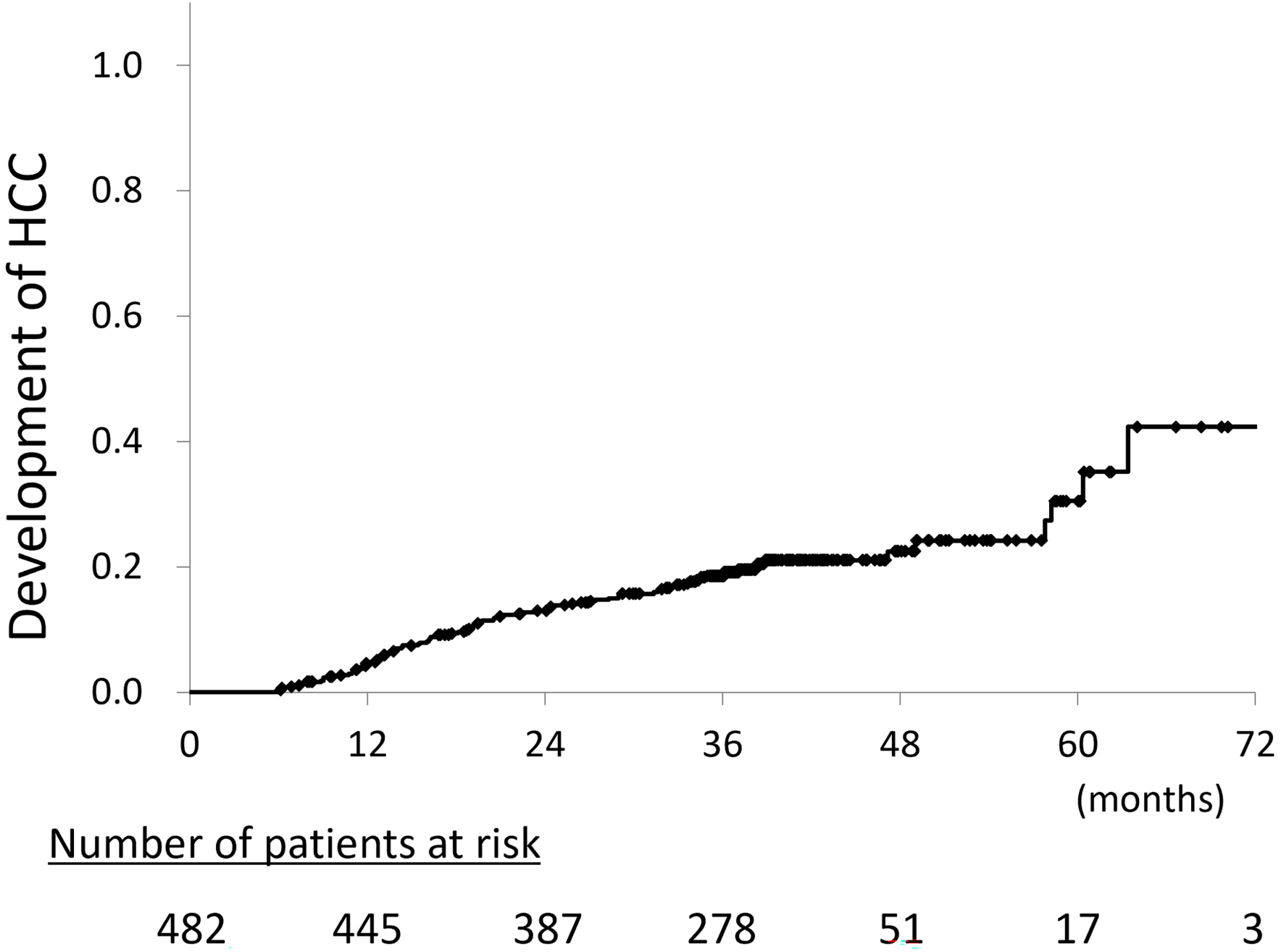
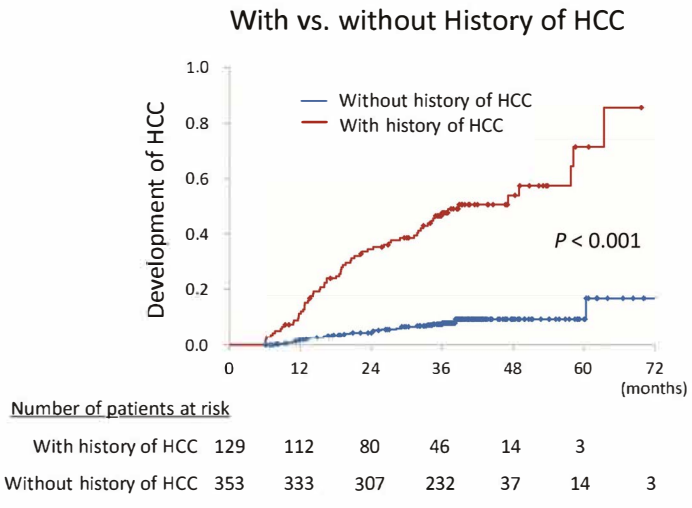
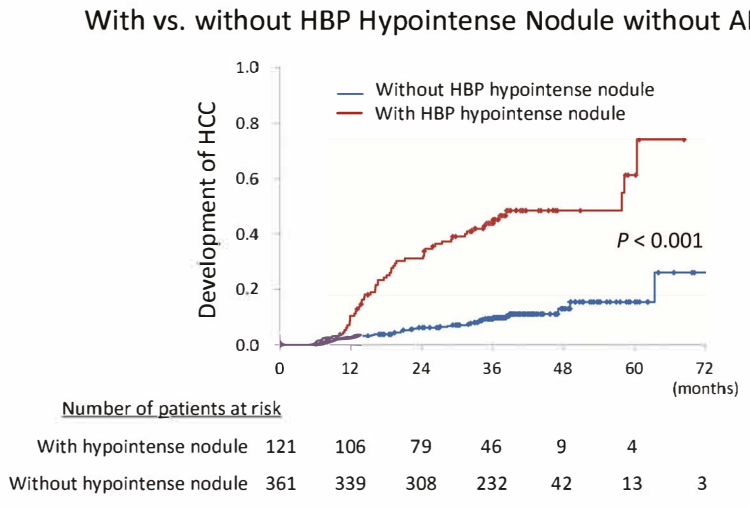
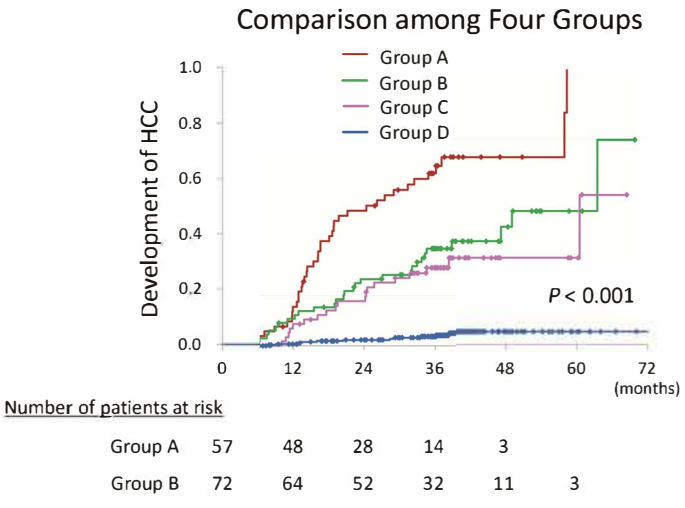
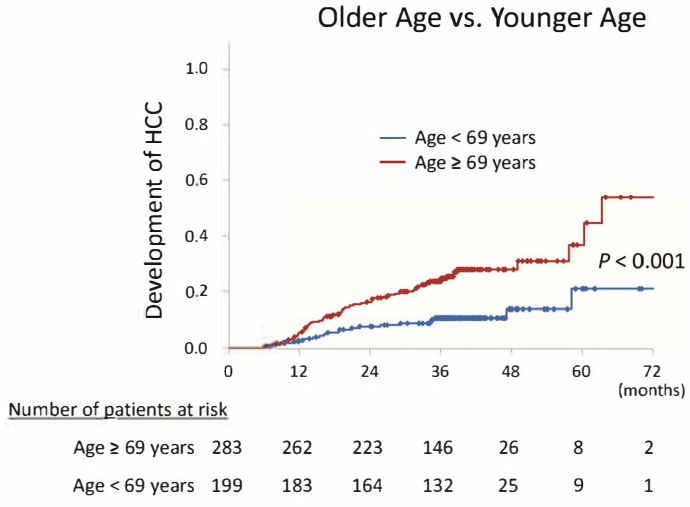

Development of HCC
1.0
0.8
0.6
0.4
0.2
0.0
0
12
24
36
48
60
72
(months)
Number of patients at risk
482
445
387
278
51
17
3

Figure 3


With vs. without History of HCC
Development of HCC
Without history of HCC
With history of HCC
P < 0.001
(months)
Number of patients at risk
With history of HCC 129 112 80 46 14 3
Without history of HCC 353 333 307 232 37 14 3


With vs. without HBP Hypointense Nodule without APHE
Development of HCC
Without HBP hypointense nodule
With HBP hypointense nodule
P < 0.001
(months)
Number of patients at risk
With hypointense nodule 121 106 79 46 9 4
Without hypointense nodule 361 339 308 232 42 13 3


Comparison among Four Groups
Development of HCC
Group A
Group B
Group C
Group D
P < 0.001
(months)
Number of patients at risk
Group A 57 48 28 14 3
Group B 72 64 52 32 11 3
Group C 64 58 51 32 6 4
Group D 289 275 256 200 31 10 3


Older Age vs. Younger Age
Development of HCC
Age < 69 years
Age ≥ 69 years
P < 0.001
(months)
Number of patients at risk
Age ≥ 69 years 283 262 223 146 26 8 2
Age < 69 years 199 183 164 132 25 9 1

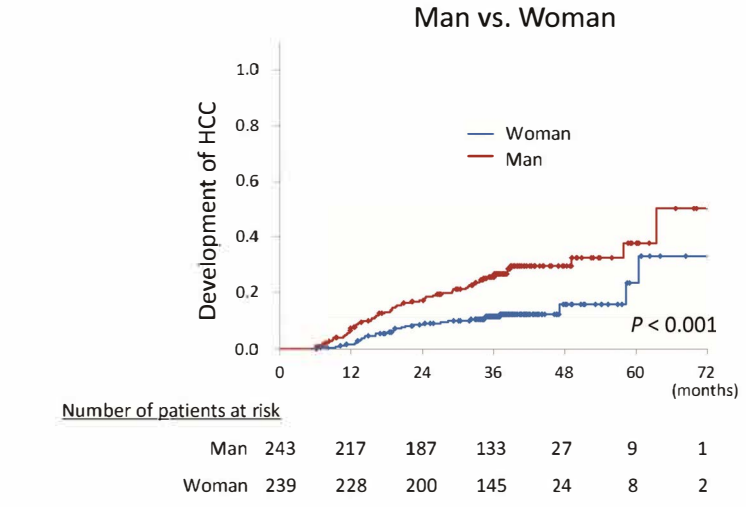

Man vs. Woman
Development of HCC
Woman
Man
P < 0.001
(months)
Number of patients at risk
Man 243 217 187 133 27 9 1
Woman 239 228 200 145 24 8 2

Figure 4

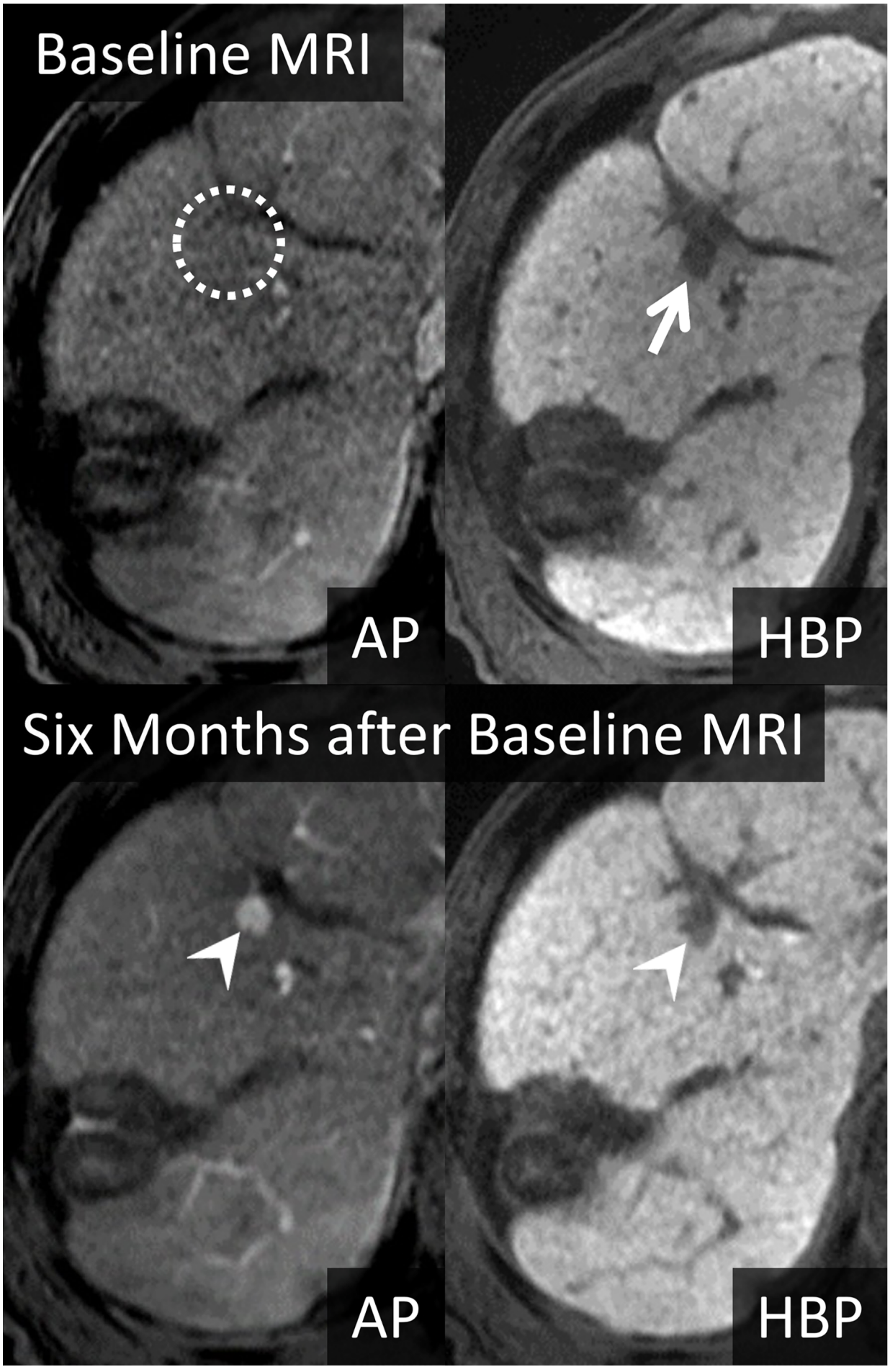


Figure 5

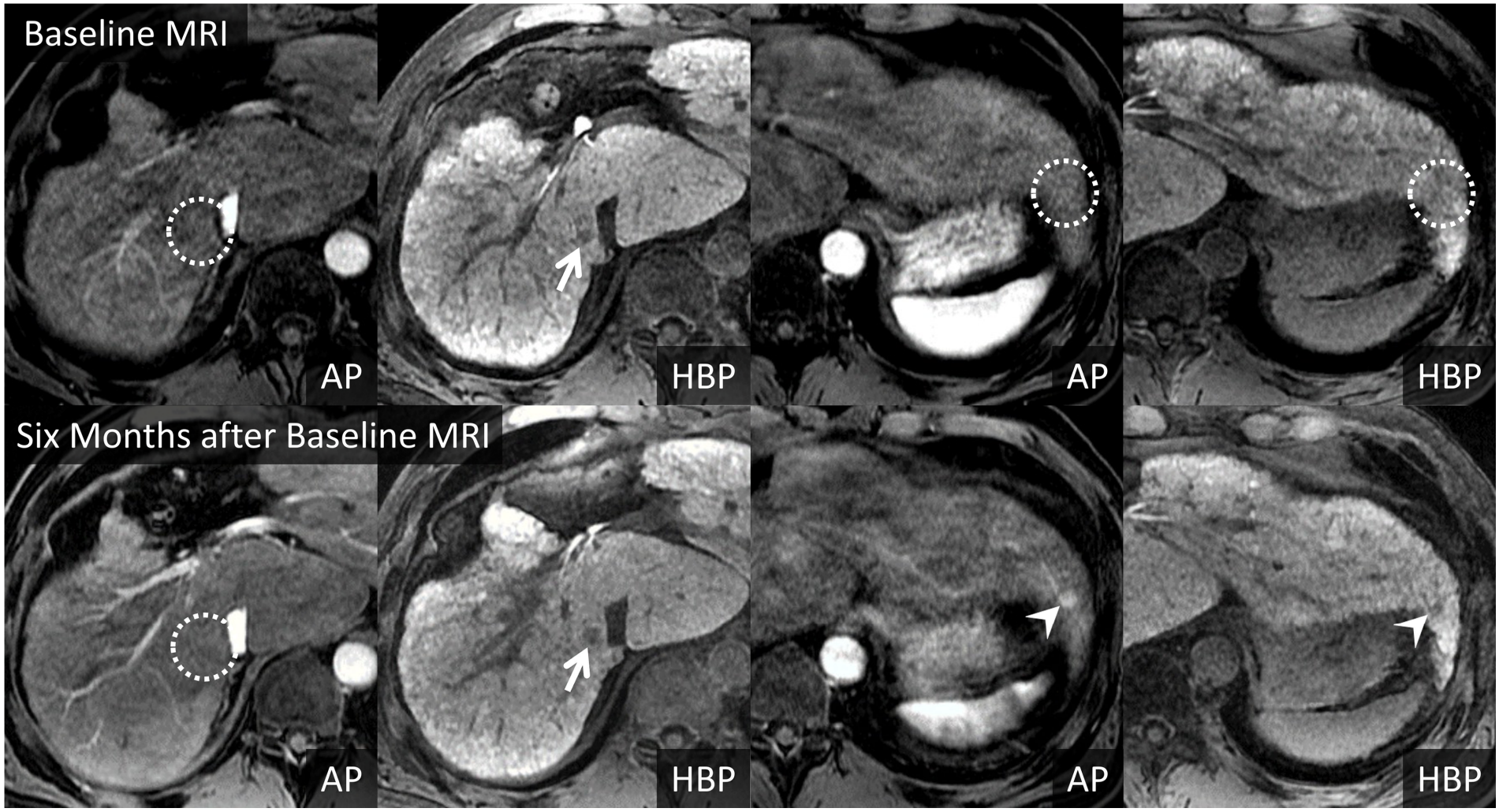
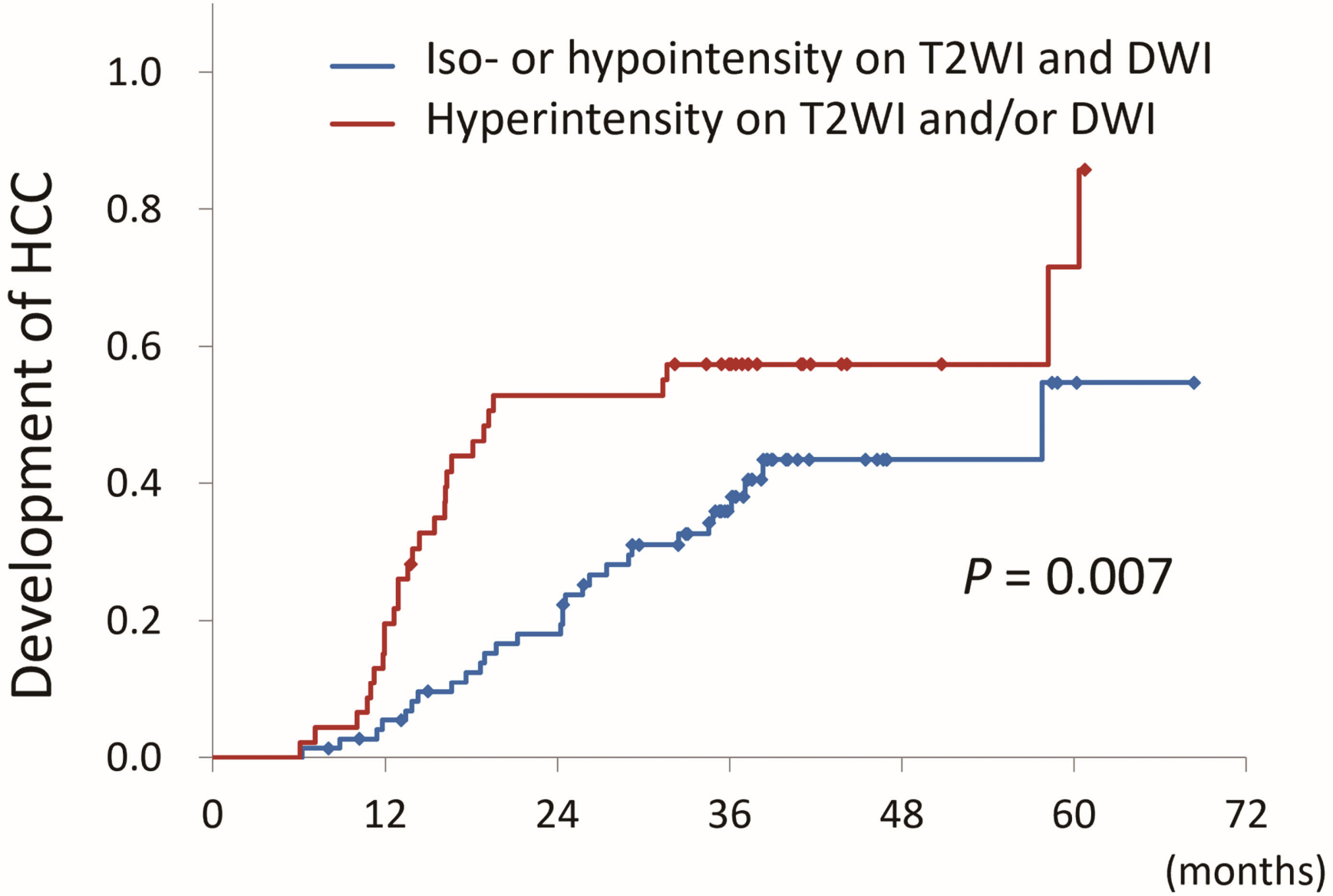

Baseline MRI
AP
HBP
AP
HBP
Six Months after Baseline MRI
AP
HBP
AP
HBP

Figure 6



Number of patients at risk

Hyperintensity	46	37	21	15	4	2
Iso- or hypointensity	75	69	58	31	5	2