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Hepatobiliary MR contrast agents are useful to diagnose hepatocellular carcinoma in patients with Budd-Chiari syndrome

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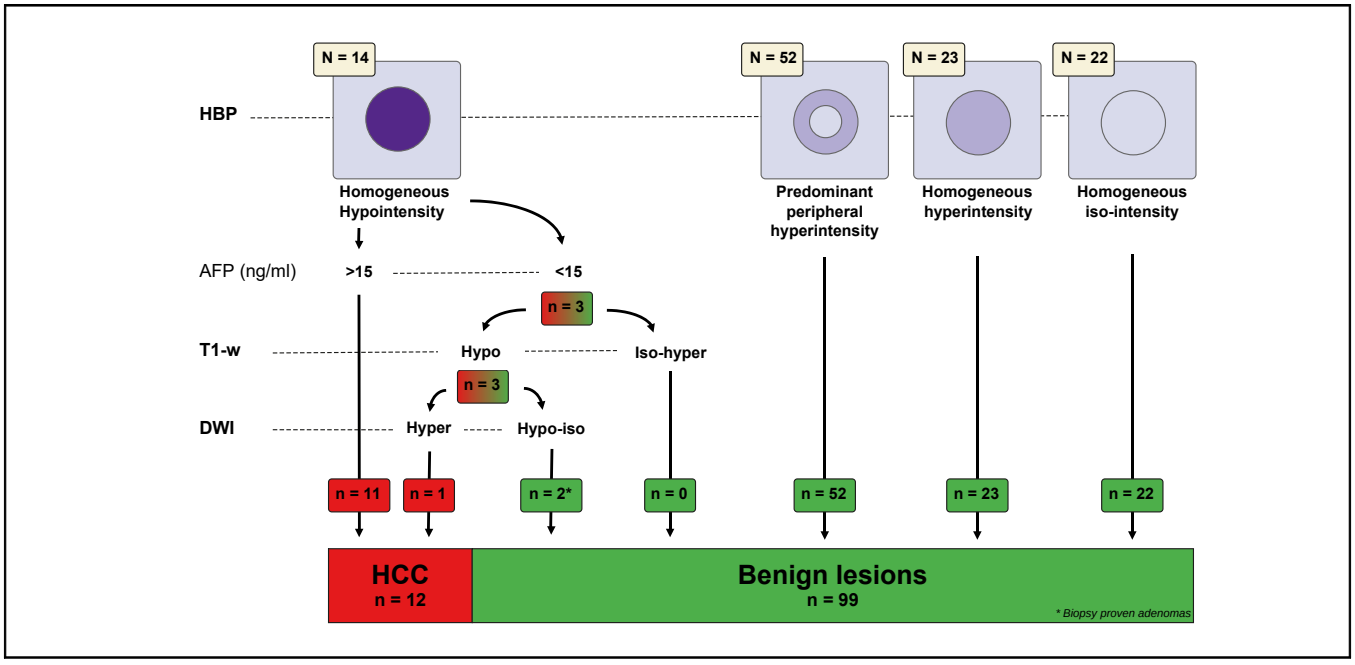
Graphical abstract



Highlights

- Most benign lesions showed homogeneous or peripheral hyperintensity on hepatobiliary phase images.
- All HCCs were homogeneously hypointense on hepatobiliary phase images.
- Hepatobiliary images are helpful to differentiate between benign lesions and HCCs in patients with Budd-Chiari syndrome.
- In patients with AFP serum levels >15 ng/ml, lesions with signal hypointensity on hepatobiliary phase were all HCCs.

Lay summary

Hepatobiliary phase imaging is an approach that has recently been shown to discriminate between benign and malignant lesions in the liver. However, it was not known whether this imaging approach could be used effectively in patients with Budd-Chiari syndrome. Herein, we have shown that hepatobiliary phase imaging appears to be useful for differentiating between benign and malignant liver lesions in patients with Budd-Chiari syndrome.

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Research article

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Hepatobiliary MR contrast agents are useful to diagnose hepatocellular carcinoma in patients with Budd-Chiari syndrome

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Background & Aims: Hepatobiliary phase (HBP) images can discriminate between benign and malignant liver lesions, but it is unclear if this approach can be used in patients with Budd-Chiari syndrome (BCS). Thus, we aimed to assess the diagnostic utility of HBP images in patients with BCS.

Methods: This retrospective study included all patients admitted to our institution with a diagnosis of BCS and focal liver lesions on hepatobiliary contrast agent-enhanced MR imaging (HBCA-MRI) from 2000 to 2019. MR images were reviewed by 2 radiologists blinded to the diagnosis of the lesions. Patient and lesion characteristics were recorded, focusing on HBP imaging features.

Results: Twenty-six patients (mean 35 ± 11 years old [13–65]; 21 women [81%] 35 ± 12 years old [13–65]; 5 men [19%] 36 ± 10 years old [19–44]) with 99 benign liver lesions and 12 hepatocellular carcinomas (HCCs) were analyzed. Patients with HCC were significantly older than those with benign lesions (mean 50 ± 10 *vs.* 33 ± 9 years old, $p = 0.003$), with higher alpha-fetoprotein (AFP) levels (3/4 [75%] *vs.* 1/22 [5%] with AFP >15 ng/ml, $p < 0.001$). Homogeneous hypointense signals were identified on HBP in 14 lesions, including 12/12 (100%) HCCs, and 2/99 (2%) benign lesions ($p < 0.001$). Most benign liver lesions showed either peripheral (n = 52/99 [53%]) or homogeneous hyperintensity (n = 23/99 [23%]) on HBP. Lesions with signal hypointensity on HBP in patients with AFP serum levels >15 ng/ml were all HCCs.

Conclusion: Most benign lesions showed homogeneous or peripheral hyperintensity on HBP images while all HCCs were homogeneously hypointense. HBP images are helpful to differentiate between benign lesions and HCCs and outperform other sequences. They should be systematically acquired for the characterization of focal lesions in patients with BCS.

Introduction

Primary Budd-Chiari Syndrome (BCS) is a rare vascular disorder involving hepatic venous outflow impairment at any level between the small hepatic veins and the right atrium.[1–4]

Chronic BCS leads to the development of focal liver lesions that can either correspond to large benign regenerative lesions—frequently referred to as 'focal nodular hyperplasia-like' (FNH-like) lesions[5]—or to hepatocellular carcinoma (HCC).[6–9] It is therefore of the highest clinical importance to accurately characterize hepatic lesions in patients with BCS, to adapt patient management.

Studies have shown that although clinical characteristics and laboratory tests, especially alpha-fetoprotein serum levels, can be useful to identify patients with HCC,[6] they are not effective in characterizing individual lesions. Thus, imaging, especially MRI, could be useful as the first non-invasive step in the characterization process. Published series have shown that most benign and malignant lesions appear markedly hyperenhanced on contrast-enhanced CT or MRI during the arterial phase.[10–12] Washout has been considered helpful in discriminating benign from malignant tumors based on the imaging hallmark for HCC that was developed and validated in patients with cirrhosis.[13,14] Unfortunately, Van Wettere *et al.* recently showed that the value of washout was limited since it was observed in close to one-third of benign liver lesions larger than 1 cm, resulting in an unacceptably low specificity for the diagnosis of HCC.[15]

Hepatobiliary contrast agents (HBCA) are gadolinium chelates that are taken up by functioning hepatocytes. Their internalization is mediated by organic anionic transporting polypeptides

Keywords: Imaging; non-invasive; vascular liver disease; liver cancer; HCC; tumor; MRI.

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(OATP) expressed on the sinusoidal membrane of functional hepatocytes. It has been shown that most (>90%) FNHs are iso or hyperintense on hepatobiliary phase (HBP) sequences,[16–21] while tumors containing altered hepatocytes—hepatocellular adenoma and HCC—are hypointense on HBP sequences.[22,23] Therefore, HBP images have been shown to be useful to discriminate FNH from other liver tumors,[17,24] explaining why they are now routinely used in a large number of expert centers.

Nevertheless, it is unclear if this approach can be used in patients with primary BSC. Only a few case reports have been published reporting FNH-like lesions showing peripheral hyperintensity on HBP,[25,26] but there are no studies assessing the diagnostic value of HBP to discriminate between HCC and benign regenerative lesions in BCS.

The aim of this study was to retrospectively evaluate the value of HBP images to discriminate benign from malignant lesions in patients with primary BCS.

Materials and methods

Patient population

This single-center retrospective study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the appropriate institutional review committee. The requirement for written informed consent was waived.

All patients admitted to our tertiary center for vascular liver disorders (Beaujon University Hospital, Clichy, France) between 2000 and 2019 with a diagnosis of primary BCS were retrieved from our prospective electronic database. Inclusion criteria were i) the diagnosis of acute, subacute or chronic BCS, and ii) initial diagnosis and follow-up including at least 1 contrast-enhanced MRI with hepatobiliary contrast agents. BCS was defined as hepatic venous outflow impairment at any level between the small hepatic veins and the right atrium.[4] The date of the diagnosis of BCS was that of the first imaging examination demonstrating obstructed venous outflow.

All available MRI examinations were screened by 2 abdominal radiologists (L.P. and L.R. with 5 years of experience) in all patients and only those showing at least 1 focal liver lesion (defined as a round, well-circumscribed lesion >10 mm in diameter seen on unenhanced or contrast-enhanced sequences) were retained. The cut-off value of 10 mm was based on a previous study from our group showing that all lesions <10 mm were benign.[15] Patients with no focal liver lesions on MRI were excluded. Patients with benign liver lesions and less than 12 months of follow-up were also excluded (Fig. 1). Demographic, clinical, laboratory, and outcome data were retrieved from patient medical records. Patients were tested for prothrombotic factors including myeloproliferative neoplasm associated with the JAK-2 or CALR mutations, paroxysmal nocturnal hemoglobinuria, coagulation disorders, antiphospholipid syndrome, and Behçet's disease. Oral contraception and pregnancy were thrombotic risk factors. A history of endovascular treatment (stenting of hepatic veins or transjugular intrahepatic portosystemic shunts [TIPS]) was also recorded.

The final population included 26 patients (mean age 38 ± 12 years old [15–65]; 21 women [81%], 38 ± 13 years old [15-65]; and 5 men [19%] 39 ± 10 years old [24–47]).

MRI protocol

Various MRI devices were used for scans because some of the patients were referred to our center with their own MR examinations. All patients had at least 1 MRI performed in our

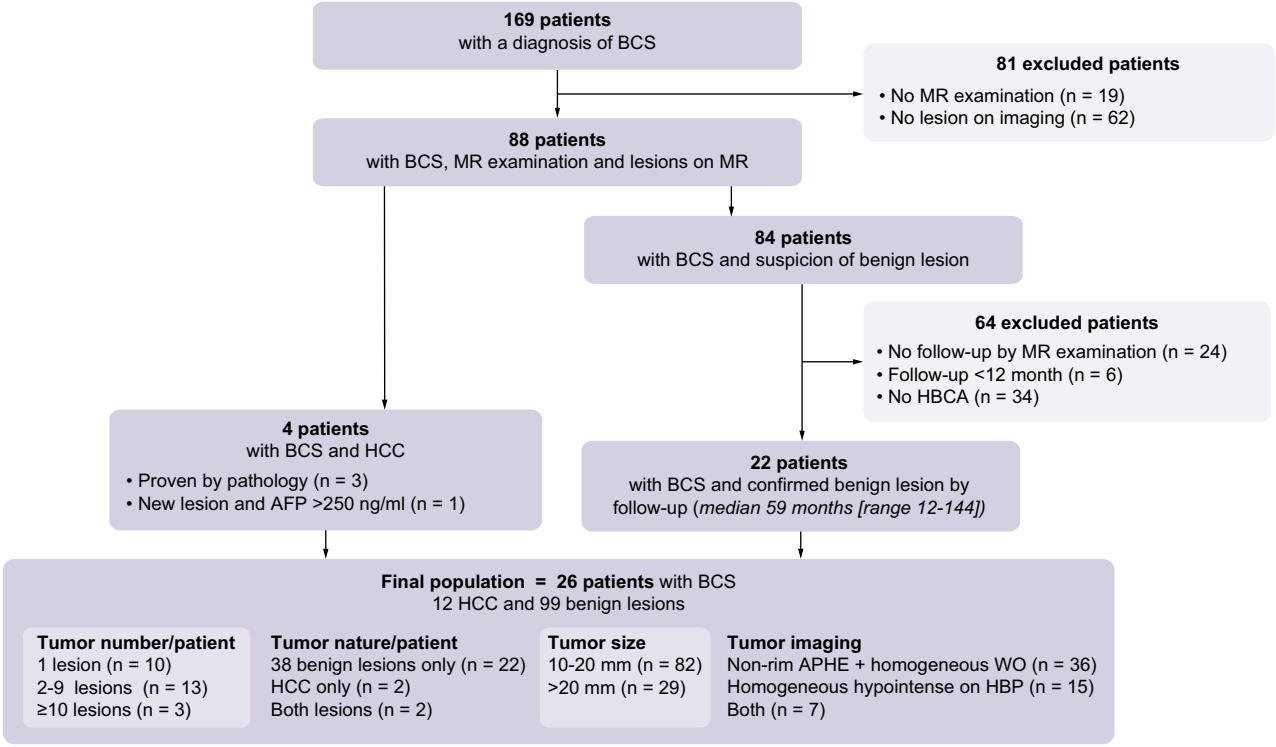

Fig. 1. Flow chart of the study. AFP, alpha-fetoprotein; APHE, arterial phase hyperenhancement; BCS, Budd-Chiari syndrome; HBP, hepatobiliary phase; HCC, hepatocellular carcinoma; WO, washout.

institution. MRI was performed in our institution on a 1.5 T clinical MR system until December 2012 and thereafter until March 2019 on a 3 T clinical MR system (Intera, Philips Medical System, Best, The Netherlands) using a phased-array body coil. All patients included had a standard liver MR exam including the following axial plane sequences: a respiratory-triggered fat-suppressed fast spin-echo T2-weighted sequence, an in- and opposed-phase gradient-echo T1-weighted sequence, a free breathing diffusion-weighted sequence with a b value of >400 s/mm^2, a fat-suppressed 3D gradient-echo T1 weighted sequence, before and after intravenous injection of Gd-BOPTA at a dose of 0.05 mmol/kg of body weight followed by a 20 ml saline solution flush administered at 2 and 1 ml/s, respectively, obtained at the arterial (bolus triggering), portal (50 s), delayed (3 min) and hepatobiliary (2 h) phases. Contrast agents and saline were injected with a power injector (Medrad; Pittsburgh, PA, USA).

Image analysis

MRI examinations with focal liver lesions were retrospectively reviewed by consensus by 2 abdominal radiologists (MVW and MR with 5 years and 11 years of expertise, respectively) on a picture archive and communication system (PACS) workstation (Carestream Health, Rochester, NY, USA). Readers were aware of the diagnosis of BCS but blinded to the nature of the liver lesions, and patient clinical and biological data.

Readers recorded the following items: i) number of liver lesions; ii) lesion location according to the Couinaud classification; iii) largest diameter of the lesion (in mm); iv) signal intensity on phase gradient-echo T1-weighted images; v) signal intensity on T2-weighted images; vi) signal intensity on arterial phase, portal venous, and delayed phase images; vii) signal intensity on hepatobiliary phase images; viii) signal intensity on high b value diffusion-weighted images; ix) fat component (present or absent) defined as signal drop in the lesion on opposed-phase T1-weighted GRE compared to in-phase T1-weighted GRE images. In patients with more than 10 liver lesions, only the largest 10 were included in the analysis.

For items 4 to 8, lesions were compared to the surrounding liver parenchyma and the presence of hypo, iso, or hyperintense areas defined as areas that showed lower, similar, or higher signal intensity than the liver, respectively. Lesions showing signal hyperintensity on arterial phase sequences were considered to have arterial phase hyperenhancement (APHE), which was further subclassified as being homogeneous, predominantly peripheral, or predominantly central. APHE was assessed on subtracted images in lesions showing signal hyperintensity on precontrast T1-weighted sequences. On precontrast T1-weighted, T2-weighted and other contrast-enhanced images, including portal venous, delayed phase, and hepatobiliary phases, lesions were described as homogeneously iso-intense, homogeneously hyperintense, homogeneously hypointense, or predominantly peripherally hyperintense. A "washout appearance" was considered to be present if a lesion was hypointense on portal venous and/or delayed phase images compared to the surrounding liver parenchyma. Washout was classified as homogeneous if it involved the entire lesion. It was considered predominantly peripheral if the periphery showed washout while the center did not.

Final diagnosis

Lesions were diagnosed based on histopathological analysis of specimens obtained by surgical resection or percutaneous biopsy, or on the basis of clinical and biological data combined with at least 12 months of follow-up. The diagnosis of HCC was based on atypical cytological and architectural features at histological examination, serum AFP levels >250 ng/ml, or both. Indications for focal liver lesion biopsy were i) a focal lesion associated with AFP serum levels >15 ng/ml; ii) lesion modification, *i.e.* appearance of previously absent washout, or ≥50% increase in size in ≤6 months; iii) a >10 mm lesion showing arterial phase hyperenhancement and washout and ancillary imaging features, especially mild-moderate signal hyperintensity on T2-weighted images or signal hyperintensity on high b value diffusion-weighted images. Criteria for benign lesions included an absence of malignant morphological features with findings suggesting benign regenerative lesions on histological examination, and/or no change or disappearance of lesions with serum AFP levels <15 ng/ml during follow-up.[6,15]

Statistical analysis

Categorical data were expressed as frequencies and percentages, and continuous variables as means and standard deviations, or medians and ranges, as suitable. A Fisher exact test or a Chi-square test was used to compare frequencies. The McNemar test was used to consider the presence of multiple lesions in some patients, when necessary. A Student's *t* test or Mann-Whitney *U* test was used to compare continuous variables according to the distribution of data. A *p* value of 0.05 was considered significant and all tests were 2-sided. All analyses were performed using the Statistical Package for the Social Sciences (SPSS) software (version 24.0. SPSS Inc., Chicago, IL, USA).

Results

Patient population and lesions

The characteristics of the 26 patients included in the study are presented in Table 1.

The etiology of BCS was identified in 18 patients (69%), most of whom had myeloproliferative neoplasms (n = 14, 54%). Seven

Table 1. Baseline characteristics of the 26 patients with primary Budd-Chiari syndrome and focal liver lesions.

Characteristics	Values
Women (%)	21 (81)
Mean age ± SD (range)	
Overall	35 ± 11 (13–65)
Women	34 ± 12 (13–65)
Men	36 ± 10 (19–44)
Prothrombotic risk factors*	
Myeloproliferative neoplasm (Jak2+)	14 (54)
Hemoglobinuria	0 (-)
Behçet's disease	1 (4)
Coagulation disorder	4 (15)
Antiphospholipid syndrome	4 (15)
Unknown	8 (31)
Oral contraception[a]	7 (33)
Pregnancy[a]	9 (43)
Median AFP serum level (range) ng/ml	3 (2–385,279)
Previous treatment	
TIPS	8 (35)
Hepatic vein stenting	3 (13)

Numbers in parentheses are percentages.
AFP, alpha-fetoprotein; TIPS, transjugular intrahepatic portosystemic shunt.
*The total exceeds the number of patients because some patients had multiple causes.
[a]Among female patients.

Table 2. Comparison of patients with only benign lesions and those with at least 1 HCC.

Patients	All (n = 26)	With benign lesions and no HCC (n = 22)	With HCC (n = 4)	*p* value
Mean age (SD)	34 (13–65)	33 (9)	50 (10)	0.003
Women (%)	21 (81)	18 (82)	1 (25)	1.000
Prothrombotic risk factors*				
Myeloproliferative neoplasm	14 (54)	13 (59)	1 (25)	0.306
Hemoglobinunria	0 (-)	0 (-)	0 (-)	-
Behçet's disease	1 (4)	1 (5)	0 (0)	1.000
Coagulation disorders	4 (15)	2 (9)	2 (50)	0.099
Antiphospholipid syndrome	4 (15)	3 (14)	1 (25)	0.511
Unknown	8 (31)	6 (27)	2 (50)	0.563
Oral contraception[1]	7 (33)	7 (32)	0 (-)	0.523
Pregnancy[1]	9 (43)	8 (44)	1 (100)	1.000
Median AFP serum level				
Median (range)	3 (2–385,279)	3 (2–21)	520 (2–385279)	0.060
>15 ng/ml	4 (15)	1 (5)	3 (75)	<0.001
Previous treatment				
TIPS	8 (35)	8 (36)	0 (-)	0.277
Hepatic vein stenting	3 (13)	2 (9)	1 (25)	0.408
Number of focal lesions				
Solitary	10 (38)	8 (36)	2 (50)	
Between 2 and 9	13 (68)	11 (50)	2 (50)	0.702
10 and more	3 (12)	3 (14)	0 (18)	

Numbers in parentheses are percentages. Comparisons made using McNemar test for categorical variables, and Student t-test or Mann-Whitney test as appropriate for continuous variables.
AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; TIPS, transjugular intrahepatic portosystemic shunt.
*The total exceeds 100% because some patients had multiple causes.
[1] In women.

(33%) female patients used oral contraception and 9 (43%) had had at least 1 pregnancy. Three patients (13%) had a history of hepatic vein stents and 8 patients (35%) had undergone TIPS placement.

A total of 111 focal liver lesions were analyzed, with a mean diameter of 20 ± 16 mm (10–132). Ten patients (38%) had a solitary lesion, 13/26 patients (50%) had 2 to 9 lesions, and 3/26 patients (12%) had 10 lesions or more. Twenty-two, 2, and 2 patients had only benign liver lesions, only HCC, or both, respectively. Focal lesions were located in all liver segments but were most frequent in the right liver (n = 73, 66%).

A diagnosis of HCC was confirmed in 12 lesions in 4 patients (Table S1). Two patients had a solitary lesion and 2 had between 2 and 9 lesions (including HCC and benign lesions). HCC was confirmed by histopathological examination in 3/4 (75%) patients. In the remaining patient, the diagnosis of HCC was based on the development of a new lesion together with a serum AFP level of 637 ng/ml. The diagnosis of a benign lesion was determined by biopsy for 4 lesions in 3 patients (Table S1). These patients underwent guided liver biopsy because lesions were suspected of being HCC (significant size growth and/or washout) and the final diagnosis corresponded to unclassified hepatocellular adenoma (n = 2, 2 lesions), focal nodular hyperplasia (n = 1), and low-grade dysplastic nodule (n = 1). The diagnosis of a benign lesion was based on imaging follow-up in the remaining patients (median follow-up 59 months [12–144]).

One of the patients who underwent biopsy had cirrhosis, and others had various degrees of fibrosis. One patient with an AFP serum level >15 ng/ml did not undergo biopsy (AFP = 21 ng/ml) because there was no washout in focal liver lesions, which remained stable over time (follow-up 144 months). None of the lesions that were initially considered to be benign were diagnosed as being HCC.

Comparison of patients with HCC and with benign lesions

The median time interval between the initial diagnosis and visualization of liver lesions was 17 months (0–115) in the entire population, 18 months (0–115) in patients with only benign lesions, and 10 months (0–31) in those with HCC, p = 0.540. Comparison of patients with HCC and those with benign lesions is provided in Table 2.

Patients with HCC were significantly older than those with benign lesions (mean 50 ± 10 years old [44–65] *vs.* 33 ± 9 years old [13–45], respectively, p = 0.005). They also more frequently had alpha-fetoprotein serum levels >15 ng/ml (n = 3/4 [75%] *vs.* 1/22 [5%] in patients with benign lesions, p <0.001).

Comparison of imaging features for HCC and benign lesions

The comparison of imaging features for HCC and benign regenerative lesions are provided in Table 3.

HCCs were significantly larger than benign lesions (mean 40 ± 41 mm *vs.* 17 ± 6 mm, respectively, p <0.001). Most benign liver lesions had a homogeneous (Fig. 2) or peripheral rim (Fig. S1) hyperintense signal on T1-weighted MR images (n = 83/99, 84%), while most HCC had homogeneous (Fig. 3) or peripheral hypointense signals (n = 11/12, 92%, p <0.001). The signal on T2-weighted images varied in benign lesions, with a predominantly iso-intense (n = 40/99 [40%]) or hypointense (n = 31/99 [31%]) signal. All HCCs had homogeneous hyperintense signals (p <0.001).

On arterial phase images, all HCCs and most benign lesions (n = 84/99 [85%]) showed some APHE (either homogeneous, predominantly peripheral rim or predominantly central). The distribution of enhancement patterns was not significantly different between the groups (p = 0.124, Table 3). Homogeneous washout was noted in 40 (40%) benign lesions and 11 (92%) HCC (p = 0.001).

The association of homogeneous APHE and homogeneous washout was identified in 30/99 (30%) and 6/12 (50%) benign lesions and HCCs, respectively (p = 0.169), and was associated with a sensitivity and specificity of 50% (95% CI 25–75) and 70% (95% CI 60–78), respectively, for the diagnosis of HCC.

The combination of any type of APHE (*i.e.* homogeneous, peripheral or central) with any type of washout (*i.e.* homogeneous or peripheral) was observed in 39/99 (39%) benign lesions

Table 3. Imaging findings of benign regenerative lesions and HCC.

Focal lesions	All (n = 111)	Benign lesions (n = 99)	HCC (n = 12)	*p* value
Mean size (SD)	20 (16)	17 (6)	40 (41)	<0.001
10–20 mm	82 (63)	77 (78)	5 (42)	0.007
>20 mm	29 (27)	22 (22)	7 (58)	
Signal intensity				
T1-weighted				
Hypointense and homogeneous	11 (10)	4 (4)	7 (58)	
Iso-intense and homogeneous	12 (11)	12 (12)	0 (-)	<0.001
Hyperintense and homogeneous	26 (23)	26 (26)	0 (-)	
Central hypointensity	61 (55)	57 (58)	4 (33)	
Predominant rim hypointensity	1 (1)	0 (-)	1 (8)	
T2-weighted				
Hypointense and homogeneous	31 (28)	31 (31)	0 (-)	
Iso-intense and homogeneous	40 (36)	40 (40)	0 (-)	<0.001
Hyperintense and homogeneous	22 (20)	10 (20)	12 (100)	
Central hyperintensity	18 (16)	18 (18)	0 (-)	
Diffusion-weighted on high b value				
Hyperintense	15 (14)	3 (3)	12 (100)	<0.001
Arterial phase[1]				
Iso-intense and homogeneous	15 (14)	15 (15)	0 (-)	
Homogeneous hyperenhancement	67 (60)	61 (62)	6 (50)	0.124
Rim hyperenhancement	21 (19)	16 (16)	5 (42)	
Central hyperenhancement	8 (7)	7 (7)	1 (8)	
Portal venous phase				
Hypointense and homogeneous	33 (30)	30 (30)	3 (25)	
Iso-intense and homogeneous	41 (37)	40 (40)	1 (8)	
Hyperintense and homogeneous	23 (21)	20 (20)	3 (25)	0.003
Predominant peripheral hypo	6 (5)	5 (5)	1 (8)	
Predominant peripheral hyper	8 (7)	4 (4)	4 (33)	
Delayed phase				
Hypointense and homogeneous	47 (42)	36 (36)	11 (92)	
Iso-intense and homogeneous	39 (35)	39 (39)	0 (-)	
Hyperintense and homogeneous	11 (10)	11 (11)	0 (-)	0.006
Predominant peripheral hypo	9 (8)	8 (8)	1 (8)	
Predominant peripheral hyper	5 (5)	5 (5)	0 (-)	
Hepatobiliary phase				
Hypointense and homogeneous	14 (13)	2 (2)	12 (100)	
Iso-intense and homogeneous	22 (20)	22 (22)	0 (-)	<0.001
Hyperintense and homogeneous	23 (21)	23 (23)	0 (-)	
Predominant peripheral hyper	52 (47)	52 (53)	0 (-)	
Other				
Fat content	4 (4)	3 (3)	1 (8)	0.352
Washout				
Homogenous	51 (46)	40 (40)	11 (92)	0.001
Homogeneous or peripheral	59 (53)	47 (48)	12 (100)	0.001
APHE and washout				
Homogeneous APHE and homogeneous WO	36 (32)	30 (30)	6 (50)	0.169
Homogeneous APHE and any WO	51 (46)	39 (39)	12 (100)	<0.001
Any APHE and homogeneous WO	36 (32)	30 (30)	6 (50)	0.169
Any APHE and any WO	51 (46)	39 (39)	12 (100)	<0.001
APHE, washout and hypointensity on HBP				
All homogenous	7 (6)	1 (1)	6 (50)	<0.001
Any APHE and any WO and homogeneous hypo on HBP	13 (12)	1 (1)	12 (100)	<0.001

Numbers in parentheses are percentages.
"Any APHE" referes to either homogeneous or peripheral APHE.
"Any WO" refers to homogeneous or peripheral WO.
Statistical tests: categorical variables compared with Chi-square and Fisher exact test. Means compared with the McNemar test for categorical variables, and Student's *t* test and medians with the Mann-Whitney *U* test.
AFP, alpha-fetoprotein; APHE, arterial phase hyperenhancement; HBP, hepatobiliary phase; HCC, hepatocellular carcinoma; WO, washout.
[1]Hyperenhancement was assessed on subtracted images for lesions showing signal hyperintensity on precontrast T1-weighted sequences).

and 12/12 HCCs (100%), respectively, resulting in a sensitivity and specificity of 100% (95% CI 75–100) and 61% (95% CI 51–70), respectively, for the diagnosis of HCC.

Value of the hepatobiliary phase

All HCC nodules showed homogeneous hypointensity on hepatobiliary phase acquisitions. Most benign lesions were either peripherally (n = 52/99 [53%]) or homogeneously hyperintense (n = 23/99 [23%]). The features of HCC and benign lesions differed significantly on HBP images (p <0.001). Two benign lesions (2%) were homogeneously hypointense on HBP images. Both showed homogeneous APHE, and washout was found in one. These 2 lesions corresponded to biopsy-proven unclassified hepatocellular adenomas (Table S1).

Adding a homogenous hypointense signal on HBP images to the aforementioned combinations of APHE and washout

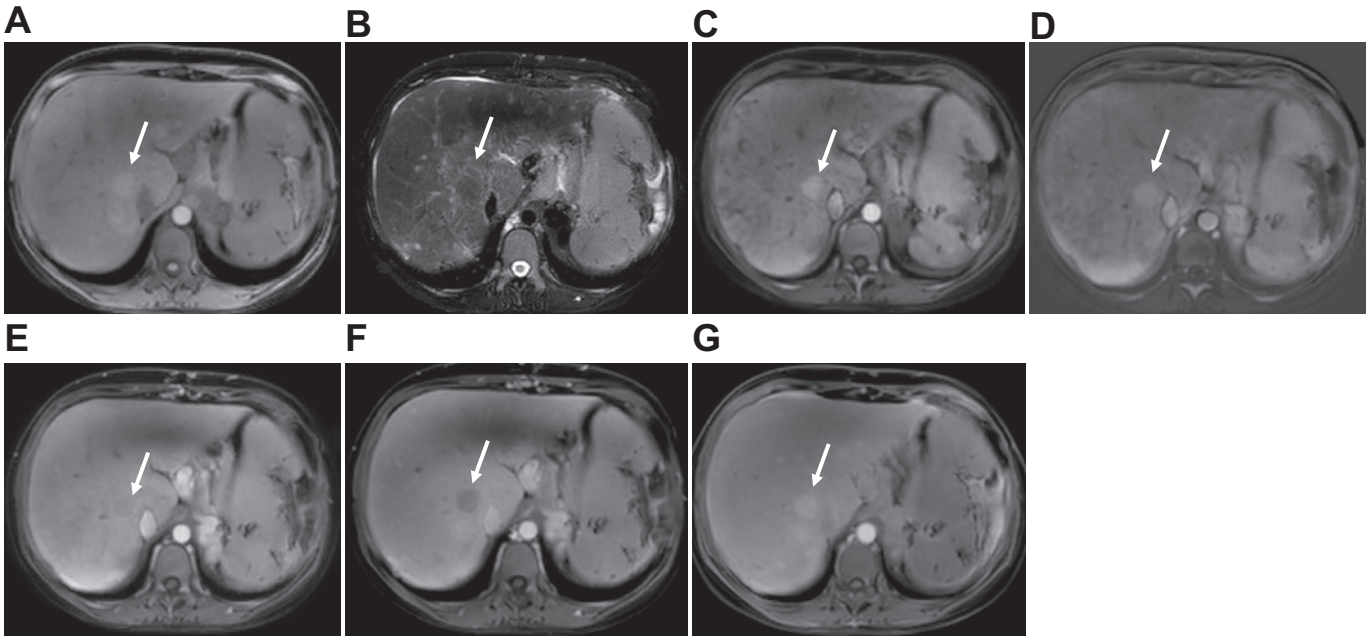

Fig. 2. Benign lesion with homogeneous hyperintensity appearance on hepatobiliary phase in 36-year-old woman with primary Budd-Chiari syndrome due to myeloproliferative neoplasm. Precontrast T1-w images (A) showed a 16 mm hyperintense lesion in the right liver. This lesion was hypointense on T2-w images (B). Intracellular gadolinium-based enhanced fat-suppressed T1-weighted GE MR images (C-D-E-F) showed arterial phase homogeneous hyperenhancement (C), confirmed by image subtraction (D), homogeneous hypointensity on portal venous phase (E) and homogeneous hypointensity on delayed phase (F). This lesion appeared homogeneous hyperintense on hepatobiliary phase (G). Serum alpha-fetoprotein was 4 ng/ml. The patient was followed-up for 12 months and remained hepatocellular carcinoma-free.

improved the diagnostic performance (Table 4). The sensitivity and specificity were 50% (95% CI 25–75) and 99% (95% CI 95–99), respectively, for the diagnosis of HCC when a homogeneous hypointense signal on HPB images was associated with homogeneous APHE and homogeneous washout. Sensitivity and specificity reached 100% (95% CI 75–100) and 99% (95% CI

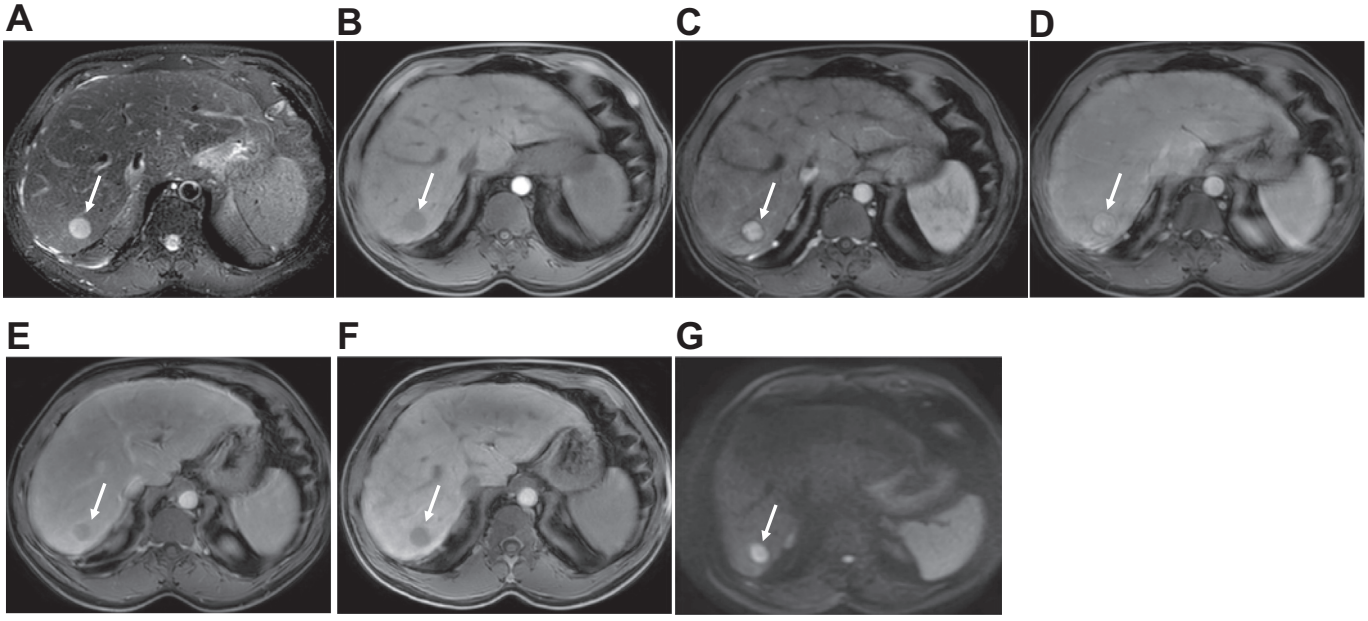

Fig. 3. HCC in a 47-year-old man with primary Budd-Chiari syndrome of unknown cause. The lesion appeared hyperintense on T2-weighted image (A). Contrast-enhanced fat-suppressed T1-weighted GE MR images showed a hypointense lesion on precontrast T1-weighted images located in the right liver (B). The lesion showed hyperenhancement on arterial phase (C), isontensity on portal venous phase (D) and washout appearance on delayed phase (E). The lesion was hypointense on hepatobiliary phase (F). The lesion appeared markedly hyperintense on high b value diffusion-weighted images (G). The serum alpha-fetoprotein level was 402 ng/ml. The patient underwent liver biopsy confirming the diagnosis of moderately differentiated HCC. The patient underwent percutaneous radiofrequency ablation. HCC, hepatocellular carcinoma.

Table 4. Diagnostic performance of imaging findings and AFP for the diagnosis of HCC.

APHE		Washout		HPB	AFP >15 ng/ml	Benign (n = 99)	HCC (n = 12)	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR− (95% CI)
Homo	Any kind	Homo	Any kind	Hypo							
Yes		Yes				30	6	50 (25–75)	70 (60–78)	1.60 (0.85–3.03)	0.73 (0.41–7.39)
Yes		Yes		Yes		1	6	50 (25–75)	99 (95–99)	49.50 (6.50–377.07)	0.50 (0.29–0.89)
Yes			Yes			33	6	50 (25–75)	67 (56–75)	1.50 (0.80–2.82)	0.75 (0.42–1.34)
Yes			Yes	Yes		1	6	50 (25–75)	99 (95–99)	49.50 (6.50–377.07)	0.50 (0.29–0.89)
	Yes	Yes				30	6	50 (25–75)	70 (60–78)	1.60 (0.85–3.03)	0.73 (0.41–7.39)
	Yes	Yes		Yes		1	6	50 (25–75)	99 (95–99)	49.50 (6.50–377.07)	0.50 (0.29–0.89)
	Yes		Yes			39	12	100 (75–100)	61 (51–70)	2.54 (1.99–3.24)	–
	Yes		Yes	Yes		1[a]	12	100 (75–100)	99 (95–99)	99.00 (14.50–695.86)	–
				Yes	Yes	2	11	92 (65–99)	98 (92–99)	45.38 (11.39–180–79)	0.09 (0.01–0.56)

"Any APHE" refers to either homogeneous or peripheral APHE. "Any WO" refers to homogeneous or peripheral WO.
AFP, alpha-fetoprotein; APHE, arterial phase hyperenhancement; Homo, homogeneous; Hypo, hypointense; LR+/LR−, positive/negative likelihood ratio; WO, washout.
[a]Corresponds to a biopsy-proven adenoma. The other biopsy-proven adenoma showed homogeneous APHE without washout, so is not included in the table.

95–99), respectively, when it was associated with any type of APHE and any type of washout.

Fig. 4 shows a diagnostic algorithm for the differentiation of HCCs and benign lesions based on HBP imaging features. Lesions with a hypointense signal on HBP images in patients with alpha-fetoprotein serum levels >15 ng/ml were all found to be HCCs (n = 11/14 hypointense lesions on HBP). Precontrast T1-weighted and diffusion-weighted images differentiated HCC (n = 1) from 2 benign lesions in the remaining 3 nodules that were hypointense on HPB images in patients with an alpha-fetoprotein serum level <15 ng/ml. The sensitivity and specificity of the combination of hypointense HBP acquisitions and AFP >15 ng/ml were 92% (95% CI 65–99) and 98% (95% CI 92–99), respectively, for the diagnosis of HCC, irrespective of the results on dynamic contrast-enhanced phases.

Discussion

Our study shows that most benign liver lesions in patients with Budd-Chiari syndrome were homogeneously or peripherally hyperintense on hepatobiliary phase images, while all HCCs were homogeneously hypointense. HBP images were found to be very helpful to discriminate benign lesions from HCCs and should systematically be acquired for the characterization and follow-up of focal lesions in patients with BCS.

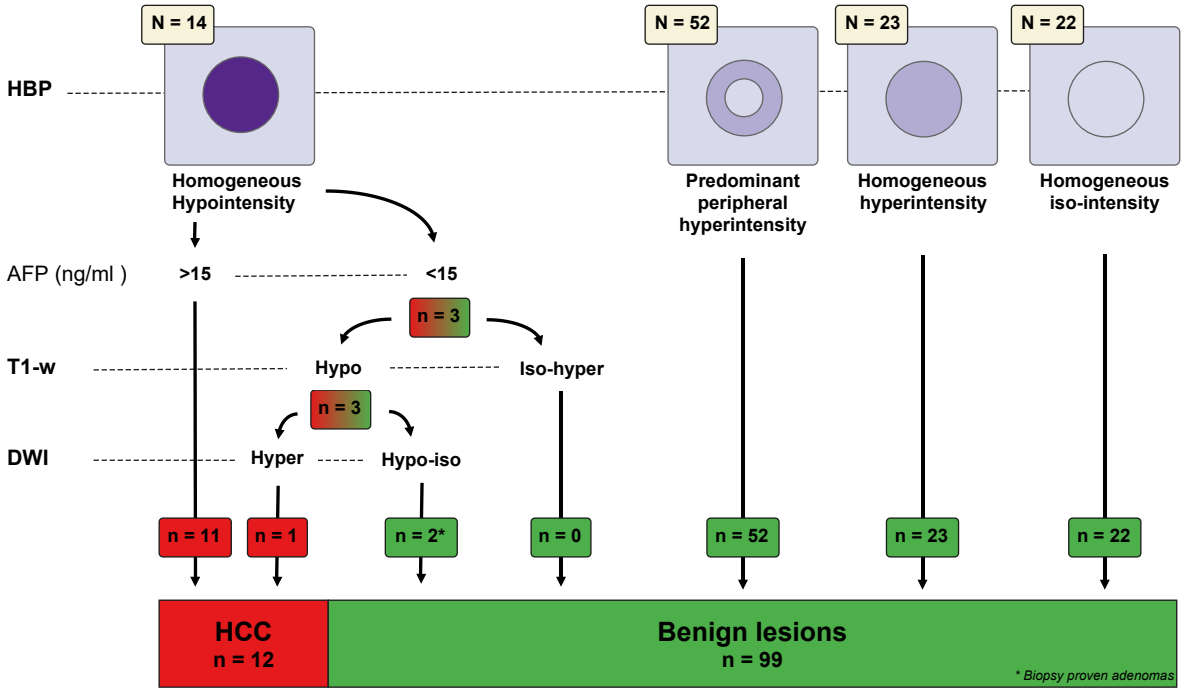

Fig. 4. Diagnostic algorithm for the differentiation between HCC and benign lesions based on the appearance of nodules on hepatobiliary phase. AFP alpha-fetoprotein, DWI, diffusion-weighted imaging; HCC, hepatocellular carcinoma; iso/hypo/hyper, iso-intense/hypointense/hyperintense; T1-w, T1-weighted imaging.

Most HCCs develop in patients with advanced fibrosis or cirrhosis, while most patients with benign hepatocellular liver lesions have normal or close to normal liver parenchyma.[27] The practical consequence is that the HCC is rarely a differential diagnosis for benign hepatocellular liver lesions. However, this is not true in BCS because this disease favors the development of both benign and malignant hepatocellular lesions. Because of the dramatically different consequences for patients, tumor characterization is of the greatest importance, and is mainly based on imaging. It is important to note that despite the different pathogeneses, both HCC and benign lesions show increased arterial perfusion, explaining why most of the lesions analyzed in the present study showed homogeneous or rim hyperenhancement in the arterial phase, in line with previous reports.[10–12,28] Thus, other features are needed to differentiate malignant from benign lesions.

Several teams, including ours, have reported differences between HCC and benign regenerative lesions in terms of the number of tumors, tumor size, and appearance on T1-, T2- or diffusion-weighted images.[10,15,29] We recently showed that the value of washout, which is traditionally associated with HCC and considered to be rare in benign hepatocellular lesions, was limited in BCS since it was observed in a significant proportion of benign lesions >1 cm, leading to an unacceptably low specificity for the diagnosis of HCC.[15] The results of the present study further validate these observations. Therefore, although imaging, and especially MRI, is helpful for the differentiation of HCC and benign liver lesions in patients with BCS, a non-invasive diagnosis is not possible in all tumors, and liver biopsy is recommended in doubtful cases. It should be noted that the aforementioned studies used extracellular contrast agents.

Several studies have shown that most HCC and hepatocellular adenomas are hypointense on HBP images,[17,23] while most focal nodular hyperplasia are homogeneously or peripherally iso-hyperintense.[18,20] Thus, liver-specific contrast agents have been shown to improve tumor characterization. The recent ESGAR consensus statement on liver MRI and the clinical use of liver-specific contrast agents states that nodule iso-hyperintensity on HBP images strongly suggests benign non-adenomatous hepatocellular lesions in the non-cirrhotic liver,[30] and that a combined interpretation of dynamic and HBP acquisitions improves the diagnostic accuracy of MRI for the detection of HCC.[30] Available data about the value of liver-specific contrast agents for BCS are limited to case reports.[25,26] Renzulli *et al.* and Newerla *et al.* reported cases of benign lesions showing hyperintense signals on HBP images.[25,26] Our results confirm these observations in a larger group. Indeed, all iso- or hyperintense lesions were benign, regardless of the presence of washout on portal venous or delayed phase images. Conversely, all HBP images were homogeneously hypointense for HCC. Of course, not all benign lesions were iso or hyperintense on HBP, since 2 adenomas showed hypointensity on HBP. This was suggested by Mamone *et al.* in a review article.[31] The main challenge is found in lesions with both arterial phase hyperenhancement (whatever the pattern) and washout. As previously shown, most of these tumors are benign but may nevertheless require liver biopsy. Our results showed that the addition of hypointense HBP images systematically increased the specificity for the diagnosis of HCC.

Moucari *et al.* reported that an AFP cut-off of 15 ng/ml had a high negative predictive value for the diagnosis of HCC.[6] Our results further validate this threshold since only 1 patient with a benign lesion had a higher value. It is important to note that the combination of AFP >15 ng/ml and a hypointense signal on HBP was associated with an excellent diagnostic performance (92% sensitivity and 98% specificity) for the diagnosis of HCC. While all studies evaluating tumor characterization in patients with BCS focus on the enhancement pattern of nodules, as well as their appearance on precontrast images, our results question the value of dynamic contrast-enhanced images and suggest that HBP images could be used to differentiate benign nodules (iso- or hyperintense) from those requiring further investigation (hypointense). This novel perspective suggests that patients with BCS with previously identified nodules could undergo abbreviated MRI protocols during follow-up.

Besides the retrospective design, our study has several limitations. First, the population was small due to our inclusion criteria, which focused on patients with primary BCS and focal liver lesions who had undergone liver-specific enhanced MR imaging. Nevertheless, the population was consecutive, well characterized, and included a large number of lesions, it is representative of a Western BCS cohort, with a majority of women and a high frequency of myeloproliferative neoplasms.[6] The recall bias cannot be excluded due to the monocentric design of the study. Also, we used Gd-BOPTA rather Gd-EOB-DTPA thus, the contrast agents might have influenced the results. However, although differences have been reported in the dynamic phases (different incidence of transient respiratory discomfort, differences between the delayed and transitional phase, *etc.*), no differences have been reported in HBP images in patients without cirrhosis. Indeed, Park *et al.* performed a head-to-head comparison with the 2 contrast agents and did not find any differences.[32] Khouri *et al.* recently suggested that Gd-EOB might be superior in cirrhotic patients, but it was mostly the case in decompensated cirrhosis.[33] Some patients with chronic BCS may develop severe liver damage that might result in cirrhosis, but it remains rare, so we believe this did not significantly influence our results. Finally, the analysis of HBP signal intensity was qualitative, which could result in subjectivity and inter-reader variability.

In conclusion, most benign hepatic lesions in patients with BCS were homogeneously or peripherally hyperintense on hepatobiliary phase acquisitions while all HCCs were homogeneously hypointense. A combination of HBP images and AFP serum level appears to be very helpful to discriminate benign lesions from HCCs and could play a central role in the follow-up strategy in patients with BCS-related nodules.

Abbreviations

AFP, alpha-fetoprotein; APHE, arterial phase hyperenhancement; BCS, Budd-Chiari syndrome; FNH, focal nodular hyperplasia-like; HBP, hepatobiliary phase; HCC, hepatocellular carcinoma; LR, likelihood ratio; OATP, organic anionic transporting polypeptides; TIPS, transjugular intrahepatic portosystemic shunt; T1-w, T1-weighted imaging; WO, washout.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contribution

Study design: M Van Wettere, M Ronot, V Vilgrain. Data collection: M Van Wettere, L Paulatto, L Raynaud, M Ronot, A Plessier, A Payancé, PE Rautou, V Paradis, D Cazals-Hatem. Data analysis: M Van Wettere, M Ronot, O Bruno, V Paraids, D Cazals-Hatem. Study coordination: M Ronot. Logistic support: M Ronot V Vilgrain. Manuscript drafting: M Van Wettere, M Ronot, Manuscript revision: All authors. Manuscript final approval: All authors.

Supplementary data

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