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Non-invasive imaging criteria for the diagnosis of hepatocellular carcinoma in non-cirrhotic patients with chronic hepatitis B

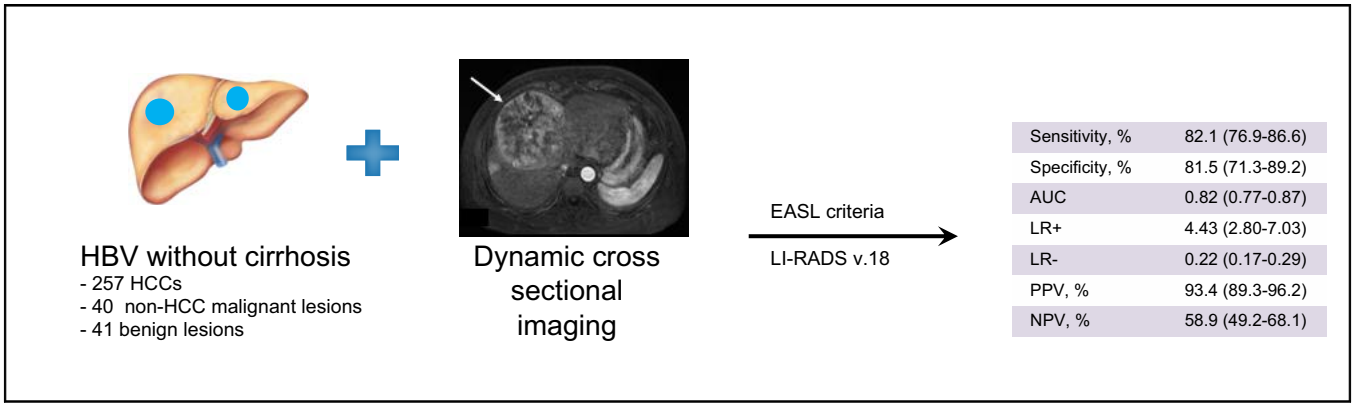
Authors

Carlos Moctezuma-Velázquez, Sara Lewis, Karen Lee, Salvatore Amodeo, Josep M. Llovet, Myron Schwartz, Juan G. Abraldes, Augusto Villanueva

Correspondence

augusto.villanueva@mssm.edu (A. Villanueva).

Graphical abstract



Highlights

- Imaging criteria defined by the EASL and LI-RADS enable the diagnosis of HCC without biopsy in patients with cirrhosis.
- A biopsy is recommended in all patients without cirrhosis.
- Imaging criteria had a good performance in patients with HBV infection without cirrhosis when pre-test probability was >70%.
- HCC may be diagnosed based solely on imaging criteria in patients with HBV subject to HCC screening (*i.e.* PAGE-B score >9).

Lay summary

Current guidelines recommend performing a biopsy to confirm the diagnosis of presumed hepatocellular carcinoma (HCC) in patients without cirrhosis. We showed that specific imaging criteria had a 100% agreement for categorizing lesions as HCC, with a positive predictive value of 93.4%. These imaging criteria could be used to diagnose HCC in HBV patients without cirrhosis with a pre-test probability of HCC of ≥70%, avoiding the need for a liver biopsy.

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Research article

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Non-invasive imaging criteria for the diagnosis of hepatocellular carcinoma in non-cirrhotic patients with chronic hepatitis B

Carlos Moctezuma-Velázquez,[1,5,7,†] Sara Lewis,[2,†] Karen Lee,[2,†] Salvatore Amodeo,[3] Josep M. Llovet,[4,5,6] Myron Schwartz,[3,4] Juan G. Abraldes,[7] Augusto Villanueva[4,*]

[1]*Department of Gastroenterology, Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán", Mexico City, Mexico;* [2]*Department of Diagnostic, Molecular and Interventional Radiology, Icahn School of Medicine at Mount Sinai, New York, NY, USA;* [3]*Department of Surgery, Icahn School of Medicine at Mount Sinai, New York, NY, USA;* [4]*Mount Sinai Liver Cancer Program, Division of Liver Diseases, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, USA;* [5]*Liver Cancer Translational Research Group, Liver Unit, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Hospital Clínic, Universitat de Barcelona, Barcelona, Catalonia, Spain;* [6]*Institució Catalana de Recerca i Estudis Avançats (ICREA), Barcelona, Catalonia, Spain;* [7]*Division of Gastroenterology (Liver Unit), Department of Medicine, University of Alberta, Edmonton, Alberta, Canada*

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Background & Aims: Criteria defined by the European Association for the Study of the Liver (EASL) and Liver Imaging Reporting and Data System (LI-RADS) enable hepatocellular carcinoma (HCC) diagnosis based on imaging in cirrhosis. Non-cirrhotic patients require biopsy given the lower pre-test probability of HCC. The objective of our study was to assess the performance of EASL and LI-RADS criteria for the diagnosis of HCC in non-cirrhotic patients with chronic HBV infection.
Methods: This was a cross-sectional study performed at a referral center. We included all patients with HBV without cirrhosis with focal liver lesions who underwent contrast-enhanced CT or MRI at our clinic between 2005-2018. Studies were reviewed by 2 radiologists blinded to the diagnosis.
Results: We included 280 patients, median age was 56.8 (IQR 48.2-65.45) years and 223 (80%) were male. In 191 (79%) cases the lesion was found as a result of screening. Cirrhosis was excluded based on pathology in 252 (90%) cases. We assessed 338 nodules: 257 (76%) HCC, 40 (12%) non-HCC malignant lesions, and 41 (12%) benign lesions. EASL criteria and LR-5/LR-tumor-in-vein (TIV) categories had a 100% agreement in categorizing lesions as HCC, and 226 nodules (67%) were classified as HCCs. The sensitivity, specificity, positive predictive value, and negative predictive value were 82.1 (76.9-86.6), 81.5 (71.3-89.2), 93.4 (89.3-96.2), and 58.9 (49.2-68.1), respectively. When the pre-test probability of HCC is >70%, estimated as a PAGE-B score above 9, and EASL or LR-5/LR-TIV criteria are met, post-test probability would be >90%.
Conclusions: EASL criteria and LR-5/LR-TIV categories show a positive predictive value in patients with HBV without cirrhosis that is comparable to that seen in patients with cirrhosis. These criteria can be used when the pre-test probability of HCC is >70%.
Lay summary: Current guidelines recommend performing a biopsy to confirm the diagnosis of presumed hepatocellular carcinoma (HCC) in patients without cirrhosis. We showed that specific imaging criteria had a 100% agreement for categorizing lesions as HCC, with a positive predictive value of 93.4%. These imaging criteria could be used to diagnose HCC in HBV patients without cirrhosis with a pre-test probability of HCC of ≥70%, avoiding the need for a liver biopsy.

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide.[1,2] The main risk factor for HCC is cirrhosis.[3] The diagnosis of HCC in patients with cirrhosis can be made through imaging.[4] This is due to a) the high pre-test probability that a nodule in a patient with cirrhosis is HCC; b) the characteristic vascular pattern of HCC as opposed to other hepatic lesions (*i.e.*, primarily dependent on the hepatic artery).[5] The European Association for the Study of the Liver (EASL)[6] and European Society for Medical Oncology[7] guidelines state that the diagnosis of HCC can be made if a given lesion larger than 1 cm in a patient with cirrhosis shows the typical hallmarks of HCC (*i.e.* arterial phase hyperenhancement and venous phase "washout") in a dynamic cross-sectional imaging study, either using CT or MRI. These criteria have a sensitivity and specificity of 72% and 90%, respectively, for lesions larger than 2 cm, and 70% and 80% for lesions between 1 and 2 cm.[8] The American Association for the Study of Liver Diseases (AASLD) has recently endorsed the use of the Liver Imaging Reporting and Data System (LI-RADS®) version 2018 criteria. LI-RADS considers other features to help stratify the likelihood that a lesion is an HCC.[9] When it comes to patients without cirrhosis all guidelines consider that the diagnosis of HCC requires histological confirmation (*e.g.* biopsy). The

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† Denotes shared first authorship
* Corresponding author. Address: Icahn School of Medicine at Mount Sinai, 1425 Madison Ave, Box 1123, Room 11-70E, New York, NY 10029, USA; Tel.: +1-212-659-9392
E-mail address: augusto.villanueva@mssm.edu (A. Villanueva).

rationale for this statement is that the pre-test probability of HCC is lower in patients without cirrhosis, with a broader spectrum of differential diagnoses.[6,7,9]

HCC surveillance is recommended in all patients with cirrhosis, regardless of the etiology. Some patients without cirrhosis also benefit from screening, such as patients with HCV infection and advanced fibrosis.[6] Some patients with HBV infection without cirrhosis are also considered at high HCC risk and included in surveillance programs.[6] A simple clinical tool, the PAGE-B score, which takes into account age, platelets, and sex, is recommended by EASL to help stratify the need for screening in patients with HBV.[6,10] This creates a paradox where the recommendation of surveillance in HBV patients without cirrhosis cannot be followed by an HCC diagnosis using imaging criteria. Indeed, there is limited evidence of the performance of these criteria in these patients. We hypothesized that imaging criteria for the diagnosis of HCC are reliable in this subgroup of patients without cirrhosis. To test this, we evaluated the performance of non-invasive cross-sectional imaging criteria using both EASL and LI-RADS in 280 patients (338 nodules) with chronic HBV without cirrhosis and a focal liver lesion.

Table 1. General characteristics of patients (n = 280).

Characteristic	
Age, years, median (IQR)	56.8 (48.2-65.45)
Male, n (%)	223 (80)
Ethnicity, n (%)	
Asian	233 (83)
White	33 (12)
African American	7 (2.5)
Other	7 (2.5)
Indication for imaging, n (%)	
Screening	191 (79)
Symptoms	29 (12)
Incidental finding	16 (6)
Abnormal liver tests	7 (3)
Type of Imaging study, n (%)	
CT	110 (39)
MRI extracellular gadolinium-based contrast agent	87 (31)
MRI gadoxetate disodium	83 (30)
Number of lesions	
Single, n (%)	232 (83)
Two, n (%)	39 (14)
Three, n (%)	9 (3)
Means of excluding cirrhosis, n (%)	
Histopathology (METAVIR scoring system)	252 (90)
Stage 0	9 (4)
Stage 1	43 (17)
Stage 2	113 (45)
Stage 3	87 (35)
FIB-4 and imaging	28 (10)
Activity grade, n (%)	
0	13 (5)
1	139 (58)
2	85 (36)
3	2 (1)
Family history of HCC, n (%)	51 (19)
NASH, n (%)	15 (6)
Diabetes, n (%)	36 (13)
Smoking, n (%)	88 (33)
Alcohol, n (%)	13 (5)
Obesity, n (%)	30 (13)
AST, U/L, median (IQR)	30 (22-40)
ALT, U/L, median (IQR)	30 (21-45)
ALP, IU/L, median (IQR)	73 (62-93)
Bilirubin, mg/dl, median (IQR)	0.6 (0.5-0.8)
Albumin, g/dl, median (IQR)	4.4 (4.1-4.6)
INR, median (IQR)	1.0 (1.0-1.0)
AFP, ng/ml, median (IQR)	10.2 (3.0-188)
Platelets, 10^9/L, median (IQR)	188 (152-235)
FIB-4, median (IQR)	1.62 (1.06-2.42)
FIB-4 ≥1.45, n (%)	155 (57)
FIB-4 >3.25, n (%)	32 (12)
HBV DNA, IU/ml, median (IQR)	0 (0-492)
HBeAg, n (%)	32/188 (17)
Current treatment, n (%)	
Tenofovir	83 (48)
Entecavir	60 (35)
Both	5 (3)
Other	24 (14)
PAGE-B score, n (%)	
Low risk (≤9 points)	49 (18)
Intermediate risk (10-17 points)	117 (42)
High risk (≥18 points)	112 (40)

AFP, alpha-fetoprotein; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; FIB-4, fibrosis 4; HCC, hepatocellular carcinoma; INR, international normalized ratio; NASH, non-alcoholic steatohepatitis.

Patients and methods

Study population and definitions

This is a retrospective cross-sectional study of diagnostic performance that included consecutive patients referred to the Liver Surgery Clinic at Mount Sinai Hospital between 2005 and 2018. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was reviewed and approved by the Institutional Review Board (HS# 18-00889) with waiver for informed consent. Inclusion criteria were presence of chronic HBV, absence of cirrhosis, presence of ≥1 liver lesion larger than 1 cm, and at least 1 dynamic cross-sectional imaging assessment, using either CT or MRI. We excluded patients according to the following exclusion criteria: patients with simple cysts, typical hemangiomas, or indeterminate pathology, if there was no definitive way to establish HCC diagnosis as detailed below, or in presence of coinfection with HCV and/or HIV. Each patient's records were reviewed to collect demographic and clinical information, including age, sex, blood tests, histological and imaging reports.

The reference standard for the diagnosis of HCC was, in order of preference: (1) pathology report available from resection specimen; (2) pathology report available from biopsy; and (3)

Table 2. Description of liver lesions (n = 338).

Liver lesions	n (%)
Hepatocellular carcinoma	257 (76)
Benign lesions:	41 (12)
Focal nodular hyperplasia	5 (1.5)
Arterioportal shunt	6 (2)
Adenoma	5 (1.5)
Complex cyst	3 (1)
Atypical hemangiomas	2 (0.6)
Angiomyolipoma	2 (0.6)
Myopericytoma	1 (0.3)
Biliary hemartoma	1 (0.3)
Granulation tissue	1 (0.3)
Telangiectatic liver nodule	1 (0.3)
Indeterminate lesions/perfusion abnormality	14 (4)
Other malignant lesions:	40 (12)
Intrahepatic cholangiocarcinoma	17 (5)
Mixed hepatocellular/cholangiocarcinoma	15 (4)
Metastases from nasopharyngeal carcinoma	3 (1)
Metastases from colorectal cancer	3 (1)
Maltoma	1 (0.3)
Sarcomatoid carcinoma	1 (0.3)

Table 3. Characteristics by type of liver lesion (n = 338).

	Benign (n = 41)	HCC (n = 257)	Malignant (n = 40)	*p* value	*p* value (HCC *vs.* MAL)	*p* value (HCC *vs.* BEN)
Demographics						
Age, median (IQR)	49.9 (38.5–57.2)	57.8 (49.7–66.1)	58.5 (46.0–66.7)	<0.001	0.8	<0.001
Male, n (%)	27 (66)	212 (82)	30 (75)	0.02	0.2	0.01
Ethnicity, n (%)				0.7		
Asian	33 (80)	214 (83)	31 (78)			
White	7 (17)	31 (12)	4 (10)			
Other	1 (3)	12 (5)	5 (12)			
Disease burden						
Single lesion, n (%)	28 (88)	182 (83)	22 (76)	0.9		
Size, cm, median (IQR)	1.6 (1.3–2.2)	3.2 (1.9–5.5)	2.5 (1.9–5.6)	<0.001	0.3	<0.001
Size >2 cm, n (%)	12 (29)	177 (69)	28 (70)	<0.001	0.8	0.8
AFP, ng/ml, median (IQR)	2.6 (2.0–3.7)	20.1 (4–305)	5.7 (2.9–38.3)	<0.001	0.007	<0.001
Assessment of fibrosis						
FIB-4 ≥1.45, n (%)	8 (19)	161 (65)	20 (53)	<0.001	0.1	0.1
METAVIR F3 on liver biopsy, n (%)	1 (8)	91 (36)	12 (35)	0.03	0.9	0.9
Risk factors for HCC						
Family history n (%)	2 (5)	53 (22)	9 (23)	0.01	0.9	0.01
Diabetes, n (%)	6 (16)	35 (14)	3 (8)	0.7		
Smoking, n (%)	7 (18)	87 (36)	16 (40)	0.02	0.9	0.6
Alcohol, n (%)	1 (3)	13 (5)	0 (0)	0.6		
Obesity, n (%)	4 (12)	22 (10)	6 (15)	0.9		
HBV DNA, IU/ml, median (IQR)	205 (0–822)	0 (0–800)	0 (0–39)	0.006	0.02	0.059
HBeAg, n (%)	7/31 (22)	30/173 (17)	3/26 (11)	0.4		
On treatment, n (%)	21 (51)	152 (59)	24 (60)	0.3		
PAGE-B: Med/High Risk, n (%)	23 (56)	222 (88)	31 (77)	<0.001	0.09	0.09
Liver tests						
AST, U/L, median (IQR)	22 (18–30)	31 (24–45)	30 (22–45)	<0.001	0.1	<0.001
ALT, U/L, median (IQR)	21 (17–34)	32 (23–45)	28.5 (21–43.5)	<0.001	0.09	<0.001
ALP, IU/L, median (IQR)	69 (58–78)	76 (63–95)	76.5 (65–105)	0.01	0.6	0.004
Bilirubin, mg/dl, median (IQR)	0.6 (0.4–0.7)	0.6 (0.5–0.8)	0.6 (0.5–0.9)	0.8		
Albumin, g/dl, median (IQR)	4.5 (4.3–4.7)	4.4 (4.1–4.6)	4.3 (4.1–4.4)	0.054		
INR, median (IQR)	1 (1–1)	1 (1–1.1)	1 (0.95–1)	0.1		
Platelets, 10^9/L, median (IQR)	215 (193–261)	181 (146–233)	183 (151.5–240)	0.001	0.6	<0.001

Kruskal-Wallis and chi-square tests. Mann-Whitney test and chi-squared were used for between-group comparisons, a Bonferroni correction was conducted to adjust the level of significance, considering a *p* value <0.025.
AFP, alpha-fetoprotein; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BEN, benign lesions; FIB-4, fibrosis 4; HCC, hepatocellular carcinoma; INR, international normalized ratio; MAL, malignant lesions.

follow-up of >24 months with no significant growth of the nodule (*i.e.* >50% growth). Chronic HBV was defined as positivity for HBV surface antigen and known diagnosis for at least 6 months. The absence of cirrhosis was a composite definition, which considered, in order of preference: (1) pathology report showing no evidence of cirrhosis on resection; (2) pathology report without cirrhosis on biopsy; (3) fibrosis-4 (FIB-4) ≤1.45 in addition to absence of imaging features of cirrhosis (*e.g.*, irregular hepatic surface) and/or portal hypertension (*e.g.*, collaterals, splenomegaly). Of note, when the reference standard for the diagnosis of HCC and/or exclusion of cirrhosis was a pathology report, the dynamic cross-sectional imaging that was assessed had to be from within the previous 3 months.

Imaging analysis

Multiphasic contrast-enhanced CT and/or MRI were performed using a variety of clinically available imaging platforms and protocols. The sequences and acquisition parameters varied slightly between different imaging platforms; however, arterial phase images were defined as those obtained 20-40 seconds after iodinated (CT) or gadolinium-based (MRI) contrast administration, portal venous phase images were defined as those obtained 60-100 seconds after contrast administration, and equilibrium/transitional phase images were defined as those obtained 3 minutes after contrast administration. MRI exams were performed using either a liver-specific gadolinium-based contrast agent (gadoxetic acid, gadoxetate disodium, Bayer Healthcare; gadobenate dimeglumine, MultiHance, Bracco Diagnostics) or other extracellular gadolinium-based contrast agents (GBCAs). In our center, our practice frequently includes the use of gadoxetate disodium agents for MRI in patients with chronic liver disease.

For qualitative analysis, 2 trained abdominal radiologists (SL and KL, with 9 and 13 years of experience in abdominal imaging, respectively) independently reviewed the CT and MR images using PACS (Centricity 3.0, General Electric Medical Systems). The reviewers were aware that the patients had HBV, however, they were unaware of any other clinicopathologic information. The index liver lesion, defined as the largest lesion identified on a single axial image or the lesion that underwent subsequent pathologic confirmation, was selected for qualitative analysis by the study coordinator. The observers recorded the segmental location and maximum size of the index lesion on portal venous phase. Dynamic contrast enhancement patterns on CT and MRI were recorded for each lesion. Liver lesions were categorized using LI-RADS v2018 and EASL criteria, described elsewhere.[6,11] For the LI-RADS classification system, the observers were allowed to use ancillary features as identified on T2-weighted imaging, diffusion-weighted imaging, or hepatobiliary phase to upgrade/downgrade LR-2, LR-3, and LR-4 lesions, when available. Discordant readings were resolved with consensus interpretation between the 2 radiologists.

Table 4. Performance of EASL or LI-RADS* criteria.

	Overall (n = 338)	≤2 cm (n = 121)	>2 cm (n = 217)
Sensitivity, %	82.1 (76.9–86.6)	71.3 (60–80.8)	87 (81.1–91.6)
Specificity, %	81.5 (71.3–89.2)	85.4 (70.8–94.4)	77.5 (61.5–89.2)
AUC	0.82 (0.77–0.87)	0.78 (0.71–0.86)	0.82 (0.75–0.89)
LR+	4.43 (2.80–7.03)	4.87 (2.29–10.33)	3.87 (2.17–6.89)
LR-	0.22 (0.17–0.29)	0.34 (0.23–0.49)	0.17 (0.11–0.25)
PPV, %	93.4 (89.3–96.2)	90.5 (80.4–96.4)	94.5 (89.8–97.4)
NPV, %	58.9 (49.2–68.1)	60.3 (46.6–73)	57.4 (43.2–70.8)
	CT (n = 134)	**MRI gadolinium (n = 96)**	**MRI gadoxetate disodium (n = 108)**
Sensitivity, %	88 (80.93.6)	74.6 (62.9–84.2)	81.4 (71.6–89)
Specificity, %	82.4 (65.5–93.2)	88 (68.8–97.5)	72.7 (49.8–89.3)
AUC	0.85 (0.78–0.92)	0.81 (0.73–0.90)	0.77 (0.67–0.87)
LR+	4.99 (2.4–10.34)	6.22 (2.13–18.14)	2.98 (1.50–5.95)
LR-	0.15 (0.080.25)	0.29 (0.19–0.44)	0.26 (0.15–0.43)
PPV, %	93.6 (86.6–97.6)	94.6 (85.1–98.9)	92.1 (83.6–97)
NPV, %	70 (53.5–83.4)	55 (38.5–70.7)	50 (31.9–68.1)

EASL, European Association for the Study of the Liver; LI-RADS, Liver Imaging Reporting and Data System; LR, likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; TIV, tumor-in-vein.
* Considering LR-5 and LR-TIV as hepatocellular carcinoma

Statistical analysis and sample size calculation

Numerical variables were summarized with median and interquartile range and categorical variables as frequencies and percentages. Comparisons between the 3 groups (*i.e.* benign, HCC, malignant) were performed with Kruskal-Wallis and chi-square tests. Mann-Whitney and chi-square tests were used for between-group comparisons, a Bonferroni correction was conducted to adjust the level of significance, considering a p value ≤0.025, based on the number of pre-planned comparisons (*i.e.* HCC *vs.* benign, and HCC *vs.* malignant). To evaluate performance of imaging criteria we computed sensitivity, specificity, positive (PPV), and negative predictive values (NPV), and positive and negative likelihood ratios. We made subgroup analysis according to the size of the lesions using a cut-off of 2 cm, depending on the type of imaging study (CT, MRI with gadolinium, or MRI with liver-specific contrast), and according to the family history of HCC. Inter-observer agreement was evaluated with Cohen's kappa and weighted Cohen's kappa for EASL and LI-RADS v2018 criteria, respectively. To assess the impact of pre-test probability on the diagnostic performance of imaging criteria we followed 2 strategies. First, since the PAGE-B score was strongly associated with the probability of HCC, we modeled the pre-test probability of HCC according to PAGE-B with logistic regression. In a second step, we assessed how the pre-test probability of HCC impacted the post-test probability of HCC after applying the imaging criteria. Our second strategy was to use the likelihood ratios of HCC to calculate the post-test probabilities of HCC according to a set of theoretical pre-test probabilities (from 0.5 to 0.9). Sample size was calculated using the confidence interval method with exact (Clopper-Pearson method) formula. Considering a prevalence of HCC of 80% in the target population, a specificity of 0.91, and a precision of 0.08, we estimated a required sample size of 306 lesions. Analyses were conducted with STATA v.14 (StataCorp, Texas, USA) and R Statistical Software (Foundation for Statistical Computing, Vienna, Austria). See supplementary CTAT Table.

Results

Characteristics of the patients

Between January of 2005 and December of 2018, we screened 934 patients with chronic HBV infection, 476 were excluded due to the presence of cirrhosis. From those patients with hepatic nodules, we excluded 36 patients due to simple cysts (n = 9), typical hemangiomas (n = 24), inconclusive histological reports (n = 3), or coinfection with HCV or HIV (n = 11). In 32 patients, we were unable to establish HCC diagnosis with acceptable certainty (see Fig. S1, which shows the flow of participants). We included

Table 5. Performance of LI-RADS Criteria (LR-4, LR-5, LR-TIV as HCC).

	Overall (n = 338)	≤2 cm (n = 121)	>2 cm (n = 217)
Sensitivity, %	88.7 (84.2–92.3)	63.8 (73.8–91.1)	91 (85.7–94.7)
Specificity, %	67.9 (56.6–77.8)	61 (44.5–75.8)	75 (58.8–87.3)
AUC	0.78 (0.73–0.84)	0.72 (0.64–0.81)	0.83 (0.76–0.90)
LR+	2.76 (2.01–3.81)	2.15 (1.45–3.18)	3.64 (2.12–6.24)
LR-	0.17 (0.11–0.24)	0.27 (0.15–0.46)	0.12 (0.07–0.20)
PPV, %	89.9 (85.4–93.2)	80.7 (70.6–88.6)	94.2 (89.5–97.2)
NPV, %	65.5 (54.3–75.5)	65.8 (48.6–80.4)	65.2 (49.8–78.6)
	CT (n = 134)	**MRI gadolinium (n = 96)**	**MRI gadoxetate disodium (n = 108)**
Sensitivity, %	89 (81.2–94.4)	85.9 (75.6–93)	90.7 (82.5–95.9)
Specificity, %	67.6 (49.5–82.6)	76 (54.9–90.6)	59.1 (36.4–79.3)
AUC	0.78 (0.70–0.87)	0.81 (0.71–0.90)	0.75 (0.64–0.86)
LR+	2.75 (1.68–4.49)	3.58 (1.77–7.24)	2.22 (1.34–3.68)
LR-	0.16 (0.09–0.30)	0.19 (0.10–0.34)	0.16 (0.07–0.33)
PPV, %	89 (81.2–94.4)	91 (81.5–96.6)	89.7 (81.3–95.2)
NPV, %	67.6 (49.5–82.6)	65.5 (45.7–82.1)	61.9 (38.4–81.9)

EASL, European Association for the Study of the Liver; LI-RADS, Liver Imaging Reporting and Data System; LR, likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; TIV, tumor-in-vein.

280 patients and 338 lesions, the characteristics of these patients can be found in Table 1. Median age was 56.8 years (IQR 48.2-65.45), 223 (80%) were male, and 233 (83%) were of Asian ancestry. The indication for imaging was surveillance in 191 (79%) patients, and 232 (83%) had a single lesion. The imaging modalities used were CT (n = 110, 39%), MRI with extracellular GBCA (n = 87, 31%), and MRI with gadoxetate disodium (n = 83, 30%). Cirrhosis was excluded based on pathology in most cases (n = 252, 90%).

Three hundred and fifty-two lesions were assessed: HCC (n = 257, 76%), malignant lesions other than HCC (n = 40, 12%), and benign lesions (n = 41, 12%). Diagnosis was confirmed by histopathology in 309 (91.4%) nodules, and by stable 24-month follow-up in the rest. A description of these lesions is shown in Tables 2 and 3. Malignant lesions were confirmed by histopathology in all cases, whereas 12 (29%) benign lesions were confirmed by histopathology. Exclusion of cirrhosis was more frequently based on histopathology for HCC and malignant lesions (249 [98%] and 38 [95%]) compared to benign lesions (11 [73%]); p <0.001). The indication for imaging was surveillance in 163 patients with HCC (74%), 28 patients with other malignant lesions (76%), and 29 patients with benign lesions (88%) (p = 0.09). The distribution of the type of imaging study (CT, MRI with extracellular GBCA, MRI with gadoxetate disodium) was not different across the groups (p = 0.5). Patients with HCCs were older (57.8 years [IQR 49.7-66.1]) than those with benign lesions (49.9 [IQR 38.5-57.2], p <0.001) and more frequently male (212, 82%) than those with benign lesions (27, 66%, p = 0.01). HCC lesions were larger (3.2 cm [1.9-5.5] *vs.* 1.6 cm [1.3-2.2], p <0.001), and had higher alpha-fetoprotein levels (20.1 ng/ml [4-305] *vs.* 2.6 ng/ml (2.0-3.7], p <0.001) than benign lesions. Regarding risk factors for HCC, family history of HCC (53 [22%] *vs.* 2 [5%], p = 0.01) was more frequent in patients with HCC when compared to benign lesions.

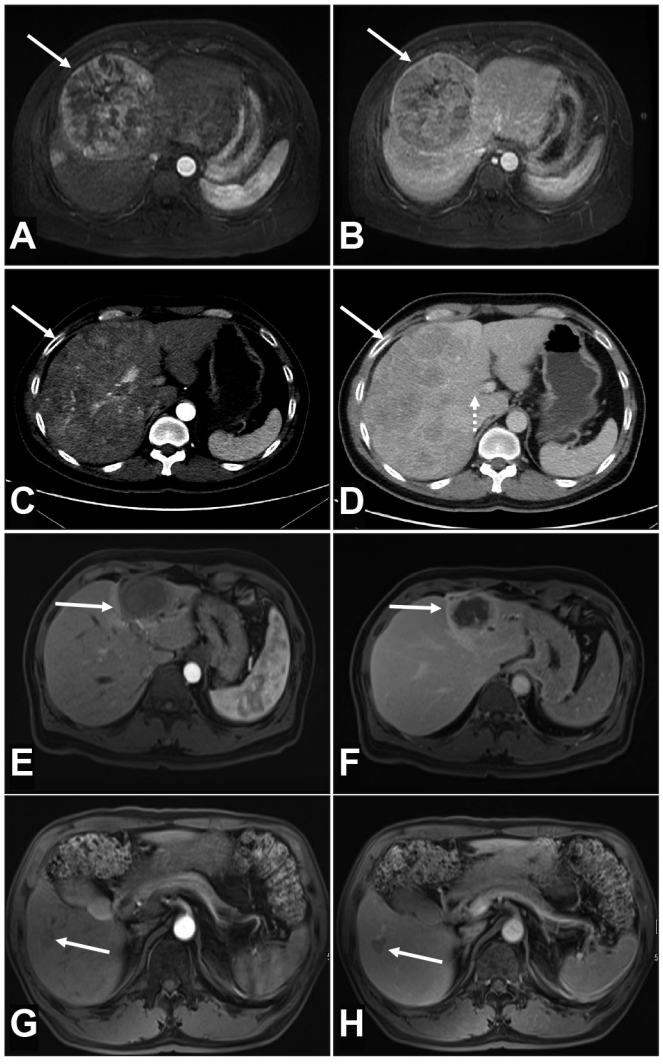

Fig. 1. Liver lesions imaging in patients with HBV using LI-RADS and AASLD criteria. (A,C,E) On arterial phase and (B,D,F) on portal venous phase. (A,B) 10.4 cm LR-5/AASLD HCC demonstrating APHE with washout and capsule on MRI. (C,D) 18.5 cm LR-TIV/AASLD HCC demonstrating infiltrative borders, APHE, washout, and tumor thrombus on CT (dashed arrow). (E, F) 5.6 cm LR-M lesion with peripheral APHE, progressive venous enhancement, and biliary distention. Pathology confirmed cholangiocarcinoma. (G, H) 1.5 cm segment 6 LR-4 lesion in a 57-year-old male, demonstrating no APHE and remaining hypointense on portal venous phase. This lesion did not meet imaging criteria for HCC but poorly defined HCC was found at subsequent resection. AASLD, American Association for the Study of Liver Diseases; APHE, arterial phase hyperenhancement; HCC, hepatocellular carcinoma; LI-RADS, Liver Imaging Reporting and Data System.

Radiological evaluation metrics and concordance between radiologists

We first assessed the performance of the radiologist in terms of concordant evaluation for both EASL and LI-RADS criteria. Cohen's kappa for EASL criteria was 0.7 (p <0.001), and weighted Cohen's kappa for LI-RADS v2018 criteria was 0.64 (p <0.001). For the 80 nodules where readings between radiologists were discordant, scans were reviewed, and a consensus reading was achieved. In the case of LI-RADS v2018, most discrepancies were in intermediate categories LR-2, LR-3, and LR-4. Only 38% and 31% of the observations that were LR-3 and LR-4 for reader A, respectively, were classified in the same way by reader B; and only 36% and 38% of the observations that were LR-2 and LR-3 for reader B, respectively, were classified in the same way by reader A.

Performance of imaging criteria to diagnose HCC in HBV without cirrhosis

Two hundred and twenty-six nodules (67%) showed arterial phase hyperenhancement and portal/venous phase "washout". EASL criteria performance had a sensitivity, specificity, PPV, and NPV of 82.1 (95% CI 76.9-86.6), 81.5 (95% CI 71.3-89.2), 93.4 (95% CI 89.3-96.2), and 58.9 (95% CI 49.2-68.1), respectively. Subgroup analysis according to size and imaging technology is depicted in Table 4. Sensitivity of EASL criteria was lower in lesions smaller than 2 cm (71.3% *vs.* 87%, p = 0.002), whereas specificity was not different (85.4% *vs.* 77.5%, p = 0.3).

The performance of LI-RADS when considering LR-5 and LR-tumor-in-vein (TIV) as HCC was identical to that obtained with EASL criteria, with a 100% agreement in categorizing lesions as HCC; 226 nodules (67%) were classified as LR-5 or LR-TIV. When grouping categories LR-4, LR-5, and LR-TIV as HCC, the computed sensitivity, specificity, PPV, and NPV were 88.7% (95% CI 84.2-92.3), 67.9% (95%CI 56.6-77.8), 89.9% (95%CI 85.4-93.2), and 65.5% (95%CI 54.3-75.5), respectively. Subgroup analysis according to size and imaging method is shown in Table 5. There were no significant differences in sensitivity and specificity according to size with the cut-off of 2 cm (sensitivity 83.8% *vs.* 91.0%, p = 0.09;

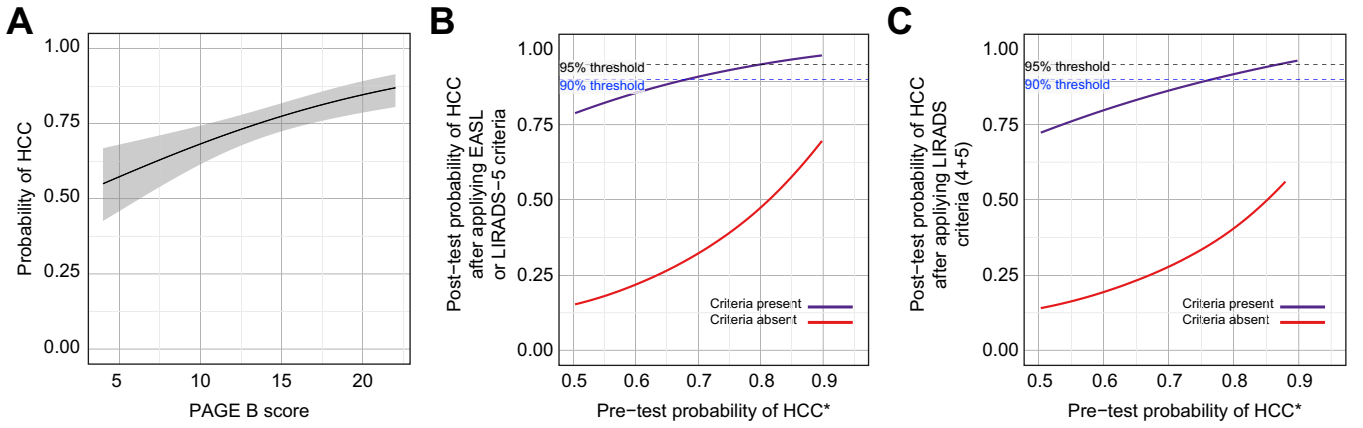

Fig. 2. Pre-test and post-test probability of HCC according to the PAGE-B. (A) Pre-test probability of HCC according to PAGE-B (estimated with a logistic regression model in which the logit = -0.20 + 0.10 * PAGE-B). (B) Post-test probability of HCC applying either EASL criteria or LR-5. With positive criteria, a threshold post-test probability of 90% is achieved when pre-test probabilities are ~70%, which equates to a PAGE-B of 10. (C) Post-test probability of HCC applying LR-4/5. A post-test probability threshold of 90% is achieved when the pre-test probability exceeds ~80%, which equates to a PAGE-B of 15. * Probabilities based on PAGE-B. EASL, European Association for the Study of the Liver; HCC, hepatocellular carcinoma.

specificity 61% *vs.* 75%, p = 0.2). LR-M for the diagnoses of malignant lesions other than HCC had a sensitivity, specificity, PPV, and NPV of 62.5% (95% CI 45.8–77.3%), 95.3% (95% CI 92.2–97.4%), 64.1% (95% CI 47.2–78.8%), and 95% (95% CI 91.9–97.2%), respectively. Fig. 1 shows some examples of liver lesions assessed according to EASL and LI-RADS.

We also analyzed the performance of imaging criteria according to the family history of HCC (see Table S1).

Impact of pre-test probability of HCC on the diagnostic performance of EASL and LI-RADS criteria

The prevalence or pre-test probability of HCC in our dataset was 76%. Since our series comes from a referral center, this might be higher than what could be expected in unselected patients with HBV without cirrhosis undergoing HCC screening in the community. We, therefore, aimed to model the performance of EASL and LI-RADS criteria in settings of lower pre-test probability.

PAGE-B has previously been shown to be strongly associated with the risk of HCC in HBV and summarizes many of the risk factors for developing HCC.[10] Indeed, this was also the case in our study (p <0.0001). The probability of HCC according to PAGE-B is shown in Fig. 2A. We subsequently assessed how EASL and LI-RADS criteria modified the pre-test probability, as estimated by PAGE-B (Fig. 2B,C). Our findings show that when the pre-test probability of HCC is >70%, estimated as a PAGE-B score above 9, and EASL or LR-5/LR-TIV criteria are met, post-test probability would be >90% (Fig. 2A). When considering both LR-4/LR-5 as diagnostic of HCC, only pre-test probabilities above 80% (*i.e.* PAGE-B ≥15) would be associated with post-test probabilities of HCC higher than 90% (Fig. 2B). Notably, even at relatively low pre-test probabilities, imaging criteria were insufficient to rule out HCC.

We further evaluated the impact of pre-test probability on the performance of imaging criteria by using the likelihood ratios of imaging criteria to calculate the post-test probabilities of HCC for theoretical pre-test probabilities ranging from 0.5 to 0.9 (see Tables S2 and S3, which show the impact of pre-test probability on the performance of imaging criteria).

Discussions

A significant number of healthcare providers use imaging criteria such as AASLD and LI-RADS criteria to diagnose HCC in HBV patients without cirrhosis, despite limited evidence on their performance in this context and that practice guidelines recommend histological confirmation in these patients.[6,7,9] In this study, we evaluated the largest cohort of non-cirrhotic HBV patients with a hepatic nodule and found that EASL criteria and LR-5/ LR-TIV categories have a PPV higher than 90% for the diagnosis of HCC. The performance in our study is similar to that reported in patients with cirrhosis and can therefore be used for imaging diagnosis without the need for liver biopsy. The performance of these criteria scales up with PAGE-B score, which encapsulates 3 of the main risk factors for HCC development. The PAGE-B score is recommended by the EASL guidelines to stratify HBV patients without cirrhosis for their risk of HCC.[6] The performance of LI-RADS for HCC diagnosis when considering categories LR-4 or LR-5 was worse than for EASL or LR-5/ LR-TIV, particularly in nodules smaller than 2 cm. This agrees with a recent meta-analysis that reported a 74% detection of HCC using LR-4 mostly in patients with cirrhosis.[12] Regarding the LR-M category for the diagnosis of cancers different from HCC, the PPV was only 64%, reinforcing the need for a biopsy in these cases. There were no significant differences in sensitivity or specificity between MRIs done with GBCA and gadoxetate disodium, probably because the diagnosis of LR-5 does not include hepatobiliary findings. However, hepatobiliary phase imaging did result in some lesions being upgraded from LR-3 to LR-4.

Few studies have evaluated the performance of imaging criteria in patients without cirrhosis, and most of them were conducted in patients without HBV. These studies have limitations in terms of the reference standard that was used to establish HCC diagnosis (*e.g.*, a 12-month follow-up to rule out HCC[13]), or how they excluded the presence of cirrhosis (*e.g.*, exclusively based on qualitative imaging features[14]). Additionally, many of them did not evaluate the false positive rate, as they only included patients with HCCs.[15] Our study is the first focused on HBV patients without cirrhosis and to include lesions other than HCC. In the study by Kim *et al.* patients with liver lesions

larger than 2 cm referred to a specialized center underwent a dynamic CT followed by either biopsy or resection.[16] They enrolled 206 patients and divided them into 3 groups: group 1 were patients with underlying cirrhosis, group 2 consisted of patients without cirrhosis but with underlying liver disease (90% had HBV), and group 3 were healthy patients with no liver disease. The prevalence of HCC in group 2 was 79%, closely resembling the 76% in our study. The performance of imaging criteria (arterial phase hyperenhancement and portal/venous phase "washout") in group 2 showed sensitivity, specificity, PPV, and NPV of 82%, 92%, 97%, and 57%, respectively, which are similar to our results. Di Martino *et al.* retrospectively evaluated the performance of imaging criteria in 85 lesions in patients without underlying liver disease (32 HCCs, 12 adenomas, 19 focal nodular hyperplasias, 12 hypervascular metastases, and 12 intrahepatic cholangiocarcinomas) and reported a sensitivity of 80-90% and a specificity approaching 100%.[17] Although predictive values were not reported, these would probably have been suboptimal based on the lower pre-test probability of HCC these patients had. Ludwig *et al.* evaluated LI-RADS v2018 criteria in 27 HCCs and 104 non-HCC primary liver cancers (*i.e.*, intrahepatic cholangiocarcinoma and mixed hepatocellular-cholangiocarcinomas) in patients without cirrhosis, mainly with HCV infection and fatty liver disease. They reported that LR-5 sensitivity and specificity for HCC were 37-67% and 97-100%, respectively. However, they excluded patients with HBV and did not include liver lesions other than HCC, which could partially explain the high specificity they found.[18] Moreover, the kappa coefficient for agreement was only 0.37, making it difficult to derive definitive conclusions on the performance of imaging criteria from this study.

Our study has some limitations, mostly inherent to its retrospective design. First, although we had histological confirmation for most nodules, more than two-thirds of benign lesions were adjudicated as non-HCC using a cut-off of 2-year size stability. This was based on reports showing an average tumor volume doubling time for HCC of 6 months.[19] However, it has recently been shown that in HBV patients without cirrhosis, HCC tends to have a relatively rapid growth rate, which would support using the 2-year size stability criteria to exclude HCC.[20] Also, although we did not exclude cirrhosis based on histopathology in all patients, we believe that the use of the combination of FIB-4 with the absence of imaging features of chronic liver disease and portal hypertension, provides a high enough NPV to confidently exclude cirrhosis in our patients.[21] Of note, we excluded cirrhosis based on histopathological grounds in the 33 patients with a FIB-4 >3.25. In addition to this, staging of fibrosis was retrieved from pathology reports, and there was no expert pathology consensus reading, but concordance between pathologists is usually very good for cirrhosis, which was the focus of our study.[22] Also, specimen adequacy was not evaluated in our study, and staging was captured as long as it had been included in the pathology report, which might have led to over and understating of fibrosis in some cases. Another potential limitation is that data for this study were derived from a single-center, and there was no validation cohort. Finally, in our series, based on patients referred to a tertiary center, the prevalence of HCC was higher (76%) than could be expected when assessing HBV patients outside of a referral center. The prevalence of LR-5 lesions was 67%, which could also be considered high, but the prevalence of LR-5 has been reported as low as 15% and as high as 63% or 80% amongst the different studies.[18,23-25] To address this, we provide a detailed analysis of the potential impact of the prevalence of HCC on the performance of EASL and LI-RADS score. Furthermore, since HCC screening in non-cirrhotic HBV is moving towards a risk-based approach, the pre-test probability of HCC in patients with a liver nodule who were selected for HCC screening based on PAGE-B or other risk scores, might approach the one observed in our study.

In conclusion, EASL criteria and LR-5/LR-TIV categories show a comparable PPV for the diagnosis of HCC in patients with chronic HBV infection without cirrhosis compared to those with cirrhosis. Thus, these imaging criteria can be used for the imaging diagnosis of HCC without the need for a liver biopsy when the pre-test probability of HCC is ≥70% (PAGE-B higher than 9).

Abbreviations

AASLD, American Association for the Study of Liver Diseases; EASL, European Association for the Study of the Liver; FIB-4, fibrosis-4; GBCA, gadolinium-based contrast administration; HCC, hepatocellular carcinoma; LI-RADS, Liver Imaging Reporting and Data System; NPV, negative predictive value; PPV, positive predictive value; TIV, tumor-in-vein.

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Conflict of interest

J.M.L. receives research support from Bayer HealthCare Pharmaceuticals, Eisai Inc, Bristol-Myers Squibb, Boehringer-Ingelheim and Ipsen; and consulting fees from Bayer HealthCare Pharmaceuticals, Merck, Eisai Inc, Bristol-Myers Squibb, Celsion Corporation, Exelixis, Eli Lilly, Roche, Genentech, Glycotest, Nucleix, Can-Fite Biopharma and AstraZeneca. Incluye mis disclosures: AV has received consulting fees from Guidepoint, Fujifilm, Boehringer-Ingelheim, FirstWord, and MHLife Sciences; advisory board fees from Exact Sciences, Nucleix, Gilead and NGM Pharmaceuticals; and research support from Eisai. CMV, SL, KL, SA, MS, and JGA have nothing to disclose.

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

Authors' contributions

CMV: conceptualization, data curation, formal analysis, investigation, methodology, software, writing – original draft. SL: data curation, investigation, methodology, software, writing – original and review/editing. KL: data curation, investigation, methodology, software, writing – original and review/editing. SA: data curation, investigation, methodology, resources, software. JML: methodology, supervision, visualization, writing – review and editing. MS: conceptualization, data curation, resources, supervision. JGA: formal analysis, methodology, software, validation, visualization, writing – review and editing. AV: conceptualization, formal analysis, methodology, project administration, supervision, validation, visualization, writing – review and editing.

Data availability statement

Deidentified patient data can be available in the setting of scientific collaborations upon request to the authors and after IRB approval.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2021.100364.

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Author names in bold designate shared co-first authorship

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