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

HBV without cirrhosis
- 257 HCCs
- 40 non-HCC malignant lesions
- 41 benign lesions

Dynamic cross sectional imaging

EASL criteria LI-RADS v.18

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.

https://doi.org/10.1016/j.jhepr.2021.100364
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,1 Josep M. Llovet,4,5,6 Myron Schwartz,3,4 Juan G. Abraldes,7 Augusto Villanueva4,*

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

JHEP Reports 2021. https://doi.org/10.1016/j.jhepr.2021.100364

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.

© 2021 The Authors. Published by Elsevier B.V. on behalf of European Association for the Study of the Liver (EASL). This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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 Oncology7 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)9 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
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.8 Some patients with HBV infection without cirrhosis are also considered at high HCC risk and included in surveillance programs.9 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 | Value |
|----------------|-------|
| 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) |
| Screening, n (%) | 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.

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

| Liver lesions | n (%) |
|----------------|-------|
| Hepatocellular carcinoma | 257 (76) |
| Benign lesions: | |
| 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 hamartoma | 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) |
| Malignant | 1 (0.3) |
| Sarcomatoid carcinoma | 1 (0.3) |

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 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)
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 as those obtained 20-40 seconds after iodinated (CT) or gadolinium-based (MRI) contrast administration, and 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 3. Characteristics by type of liver lesion (n = 338).

| Demographics | Benign (n = 41) | HCC (n = 257) | Malignant (n = 40) | p value (HCC vs. MAL) | p value (HCC vs. BEN) |
|--------------|----------------|---------------|-------------------|-----------------------|-----------------------|
| 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 (13–3.2) | 3.2 (19.5–5.5) | 2.5 (19.5–6.6) | <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 (4–30.5) | 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) | 15 (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 (63–93) | 76.5 (65–103) | 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) | 1 (0.9–1.1) | 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.
Considering LR-5 and LR-TIV as hepatocellular carcinoma (HCC) step, we assessed how the pre-test probability of HCC impacted the diagnostic performance of imaging criteria. We followed 2 strategies. First, since the PAGE-B score was strongly associated with the type of imaging study (CT, MRI with gadolinium, or MRI with gadoxetate disodium), we excluded 36 patients due to simple cysts (n = 9), typical hemangiomas (n = 24), inconclusive histological reports (n = 15), and according to the family history 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 = 2), 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 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.

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 (60.8–80.8)| 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 (2.17–6.69) |
| LR-            | 0.22 (0.17–0.29)| 0.34 (0.22–0.49)| 0.17 (0.01–0.25) |
| 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 (46.6–73.3)| 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 (71.6–89.1) |
| 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 (83.6–97.3) |
| NPV, %         | 70 (53.5–83.4)| 55 (38.5–70.7)| 50 (31.9–68.1) |

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 (0.01–0.24)| 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)| 94.3 (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 (812–94.4)| 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 (812–94.4)| 91 (815–96.6)| 89.7 (813–95.2) |
| NPV, %         | 67.6 (49.5–82.6)| 65.5 (45.7–82.1)| 61.9 (38.8–81.9) |

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.
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 gadobenate) 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.

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;
A post-test probability threshold of 90% is achieved when the pre-test probability exceeds 0.80, 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.

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. 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. 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. 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. 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), or how they excluded the presence of cirrhosis (e.g., exclusively based on qualitative imaging features). Additionally, many of them did not evaluate the false positive rate, as they only included patients with HCCs. 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. 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%. 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. 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. 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. 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. 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. 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. 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 attenuation; HCC, hepatocellular carcinoma; LI-RADS, Liver Imaging Reporting and Data System; NPV, negative predictive value; PPV, positive predictive value; TIV, tumor-in-vein.

Financial support
J.M.L. is supported by grants from the European Commission (EC) Horizon 2020 Program (HEPCAR, proposal number 667273-2), the US Department of Defense (CA150272P3), the National Cancer Institute (P30 CA186521), the Samuel Waxman Cancer Research Foundation, the Spanish National Health Institute (MICINN, SAF-2016-76390), through a partnership between Cancer Research UK, Fondazione AIRC and Fundación Científica de la Asociacion Española Contra el Cáncer (HUNTER, Ref. C9380/A26813), and by the Generalitat de Catalunya (AGAUR, SGR-1358). Funders had no involvement in the design, collection, analysis, or interpretation of data, nor in the writing of the manuscript; the work was independent of the funding.

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. Include mis disclosures: AV has received consulting fees from Guidedpoint, 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 JCA 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. J.M.L.: methodology, supervision, visualization, writing – review and editing. MS: conceptualization, data curation, resources, supervision. J.C.A.: 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.

References

Author names in bold designate shared co-first authorship

[1] Ferlay J, Laversanne M, Ervik M, Lam F, Colombet M, Mery L, et al. Global Cancer Observatory: Cancer Today, Lyon, France: International Agency for Research on Cancer; 2018. Available from: https://gco.iarc.fr/today. [Accessed 17 September 2020].
[2] Villanueva A. Hepatocellular carcinoma, N Engl J Med 2019;380:1450–1462.
[3] Kalaitzakis E, Gunnarsdottir SA, Josefsson A, Bjornsson E. Increased risk for malignant neoplasms among patients with cirrhosis. Clin Gastroenterol Hepatol 2011;9:168–174.
[4] Roberts LR, Sirlin CB, Zaimi F, Almasri J, Prokop LJ, Heimbach JK, et al. Imaging for the diagnosis of hepatocellular carcinoma: a systematic review and meta-analysis. Hepatology 2018;67:401–421.
[5] Matsui O, Kobayashi S, Sanada J, Kouda W, Ryu Y, Kozaka K, et al. Hepatocellular nodules in liver cirrhosis: hemodynamic evaluation (angiography-assisted CT) with special reference to multi-step hepatocarcinogenesis. Abdom Imag 2011;36:264–272.
[6] European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2018;69:182–236.
[7] Vogel A, Cervantes A, Chau I, Daniele B, Llovet JM, Meyer T, et al. Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. Ann Oncol 2018;29:v238–v255.
[8] Aube C, Oberti F, Lonjon J, Pageaux G, Seror O, N’Kontcho O, et al. EASL and AASLD recommendations for the diagnosis of HCC to the test of daily practice. Liver Int 2017;37:1515–1525.
[9] Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecasis MM, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American association for the study of liver dis- eases. Hepatology 2018;68:723–750.
[10] Papatheodoridis G, Dalekos G, Syppa V, Yurdaydin C, Buti M, Goulis J, et al. PAGE-B predicts the risk of developing hepatocellular carcinoma in Caucasians with chronic hepatitis B on 5-year antiviral therapy. J Hepatol 2016;64:800–806.
[11] Chernyak V, Fowler KJ, Kamaya A, Kielar AZ, Elsayes KM, Bashir MR, et al. Liver imaging reporting and data system (LI-RADS) version 2018: imaging of hepatocellular carcinoma in at-risk patients. Radiology 2018;289:816–830.
[12] van der Pol CB, Lim CS, Sirlin CB, McGrath TA, Salameh JP, Bashir MR, et al. Accuracy of the liver imaging reporting and data system in computed tomography and magnetic resonance image analysis of hepatocellular carcinoma or overall malignancy-A systematic review. Gastroenterology 2019;156:976–986.
[13] Di Martino M, Saba I, Bosco S, Rossi M, Miles KA, Di Miccio R, et al. Hepatocellular carcinoma (HCC) in non-cirrhotic liver: clinical, radiological and pathological findings. Eur Radiol 2014;24:1446–1454.
[14] Winston CB, Schwartz LH, Fong Y, Blumgart LH, Panick DM. Hepatocel- lular carcinoma: MR imaging findings in cirrhotic livers and noncirrhotic livers. Radiology 1999;210:75–79.
[15] Lin MT, Chen CL, Wang CC, Cheng YF, Eng HL, Wang JH, et al. Diagnostic sensitivity of hepatocellular carcinoma imaging and its application to non-cirrhotic patients. J Gastroenterol Hepatol 2011;26:745–750.
[16] Kim SE, Lee HC, Shim JH, Park HJ, Kim KM, Kim PN, et al. Noninvasive diagnostic criteria for hepatocellular carcinoma in hepatic masses >2 cm in a hepatitis B virus-endemic area. Liver Int 2011;31:1468–1476.
[17] Ciollina M, Di Martino M, Bruno O, Pommier R, Vilgrain V, Ronot M. Peritoneal and pleural fluids may appear hyperintense on hepatobiliary phase using hepatobiliary MR Contrast agents. Eur Radiol 2018;28:3020–3031.
[18] Ludwig DR, Faura TJ, Cannella R, Tsai R, Naem M, LeBlanc M, et al. Expanding the Liver Imaging Reporting and Data System (LI-RADS) v2018 diagnostic population: performance and reliability of LI-RADS for dis- tinguishing hepatocellular carcinoma (HCC) from non-HCC primary liver carcinoma in patients who do not meet strict LI-RADS high-risk criteria. HPB (Oxford) 2019;21:1697–1706.
[19] Ebara M, Hatano R, Fukuda H, Yoshikawa M, Sugira N, Saisko H. Natural course of small hepatocellular carcinoma with underlying cirrhosis: A study of 30 patients. Hepatogastroenterology 1998;45(Suppl 3):1214–1220.
[20] Nathani P, Gopal P, Rich N, Yopp A, Yokoo T, John B, et al. Hepatocellular carcinoma tumour volume doubling time: a systemic review and meta-analysis. Gut 2020.
[21] Xiao G, Yang J, Yan L. Comparison of diagnostic accuracy of aspartate aminotransferase to platelet ratio index and fibrosis-4 index for detecting liver fibrosis in adult patients with chronic hepatitis B virus infection: a systemic review and meta-analysis. Hepatology 2015;61:292–302.
[22] Robert M, Sofair AN, Thomas A, Bell B, Bialek S, Corless C, et al. A comparison of hepatopathologists’ and community pathologists’ review of liver biopsy specimens from patients with hepatitis C. Clin Gastroenterol Hepatol 2009;7:335–338.
[23] Lee SM, Lee JM, Ahn SJ, Kang HJ, Yang HK, Yoon JH. Diagnostic perfor- mance of 2018 KLCA-NCC practice guideline for hepatocellular carcinoma on gadoxetic acid-enhanced MRI in patients with chronic hepatitis B or cirrhosis: comparison with LI-RADS version 2018. Kor J Radiol 2021.
[24] Barat M, Nguyen TTL, Holland C, Coty JB, Hoefell C, Terris B, et al. LI-RADS v2018 major criteria: do hepatocellular carcinomas in non-alcoholic steatohepatitis differ from those in virus-induced chronic liver disease on MRI? Eur J Radiol 2021;138:109651.
[25] Min JH, Kim JM, Kim YK, Cha DI, Kang TW, Kim H, et al. Magnetic resonance imaging with extracellular contrast detects hepato- cellular carcinoma with greater accuracy than with gadoxetic acid or computed tomography. Clin Gastroenterol Hepatol 2020;18:2091–2100. e2097.