의학석사 학위논문

간경변증이 없는 만성 C 형 간염 환자의 간세포암종 진단을 위한 LI-RADS 기준의 정확성에 관한 연구

Accuracy of the LI-RADS Criteria for Diagnosis of Hepatocellular Carcinoma in Noncirrhotic Patients with Chronic Hepatitis C: A Multicenter Data Analysis

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간경화가 없는 만성 C 형 간염 환자의 간세포암종 진단을 위한 LI-RADS Criteria

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이 논문을 의학석사 학위 논문으로 제출함

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Abstract

Background and aims: Despite the known risk of HCC beyond chance, the LI-RADS criteria have not been validated for noncirrhotic patients with chronic hepatitis C (CHC). We aimed to evaluate the diagnostic performance of LR-5 observations for HCC in these patients, in comparison to their cirrhotic counterparts.

Methods: We analyzed 22 years of consecutive data from CHC patients who had focal hepatic nodules ≥1 cm on dynamic CT or MRI scans and who subsequently underwent pathologic confirmation through biopsy or resection at three university hospitals. All images were reviewed by two radiologists using the LI-RADS classification.

Results: Our study included 529 lesions from 474 patients: 239 from 223 noncirrhotic patients and 290 from 251 cirrhotic patients. The pathologies consisted of 448 HCCs, 54 other malignant masses, and 27 benign lesions. Non-HCC lesions among LR-5 observations were identified in one noncirrhotic and three cirrhotic cases. For lesions from noncirrhotic livers, the LR-5 criteria for diagnosing HCC demonstrated a sensitivity, specificity, PPV, and NPV of 82.1% (95% CI, 76.7–87.4), 97.7% (93.3–100.0), 99.4% (98.2–100.0), and 55.1% (44.1–66.2), respectively. The specificity and PPV were comparable to those of cirrhotic counterparts. Stratified analyses of noncirrhotics showed that viral and imaging factors did not affect LR-5 efficacies. Fagan's nomogram indicated that the HCC probability for LR-5 nodules exceeded 95% even in noncirrhotic patients with a low-risk aMAP score of 40, equivalent to a pre-test prevalence of 40%.

Conclusions: Given the impressive performance of the LR-5 criteria in this multicenter study, imaging alone may suffice for diagnosing HCC in noncirrhotic CHC patients, even if not at aMAP high-risk.

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Introduction

The long-lasting hepatic inflammation caused by the hepatitis C virus (HCV) frequently leads to the sequential development of advanced fibrosis, cirrhosis, and hepatocellular carcinoma (HCC).[1] However, evidence suggests that the 5-year risk for noncirrhotic HCV patients to develop HCC is 1.35–1.6%, indicating a potential direct virogenic property, possibly induced by synergistic mechanisms between viral-induced oncogenic and host-related pathways.[2, 3] Moreover, curing HCV with antiviral treatment does not entirely eradicate the risk of HCC development, even in patients without liver cirrhosis (LC).[4-6]

Current practice guidelines from various sources recommend diagnosing HCC using multiphasic CT or MRI scans without histological confirmation in high-risk patients.[7-10] These guidelines differ in their strictness or expansiveness. Until recently, non-cirrhotics infected with either hepatitis B virus (HBV) or HCV have not been considered as high-risk due to insufficient evidence regarding radiological diagnostic performance in these settings.[8]

Interestingly, the most recent update from the American Association for the Study of Liver Diseases (AASLD) policy uniquely accepts an imaging-based diagnosis of HCC without biopsy for an LR-5 lesion in patients with noncirrhotic HBV and a PAGE-B score >9.[8] This approach achieves a >90% probability of HCC, based on a recent validation of the Liver Imaging Reporting & Data System (LI-RADS) criteria for developing HCC in this specific group.[11] However, while the AASLD endorses the LI-RADS-based diagnosis for HCC, these criteria and even European recommendations have not been validated in populations with noncirrhotic HCV infection.[7, 8]

Given this context of radiological diagnosis in the face of an evident HCC risk, we undertook a comprehensive evaluation of the diagnostic performance of LI-RADS observations for HCC on dynamic CT/MRI images in noncirrhotic patients with chronic hepatitis C. We then compared these findings with pathologically-confirmed hepatic nodules from three tertiary referral centers, set against data from cirrhotic HCV patients.

Methods

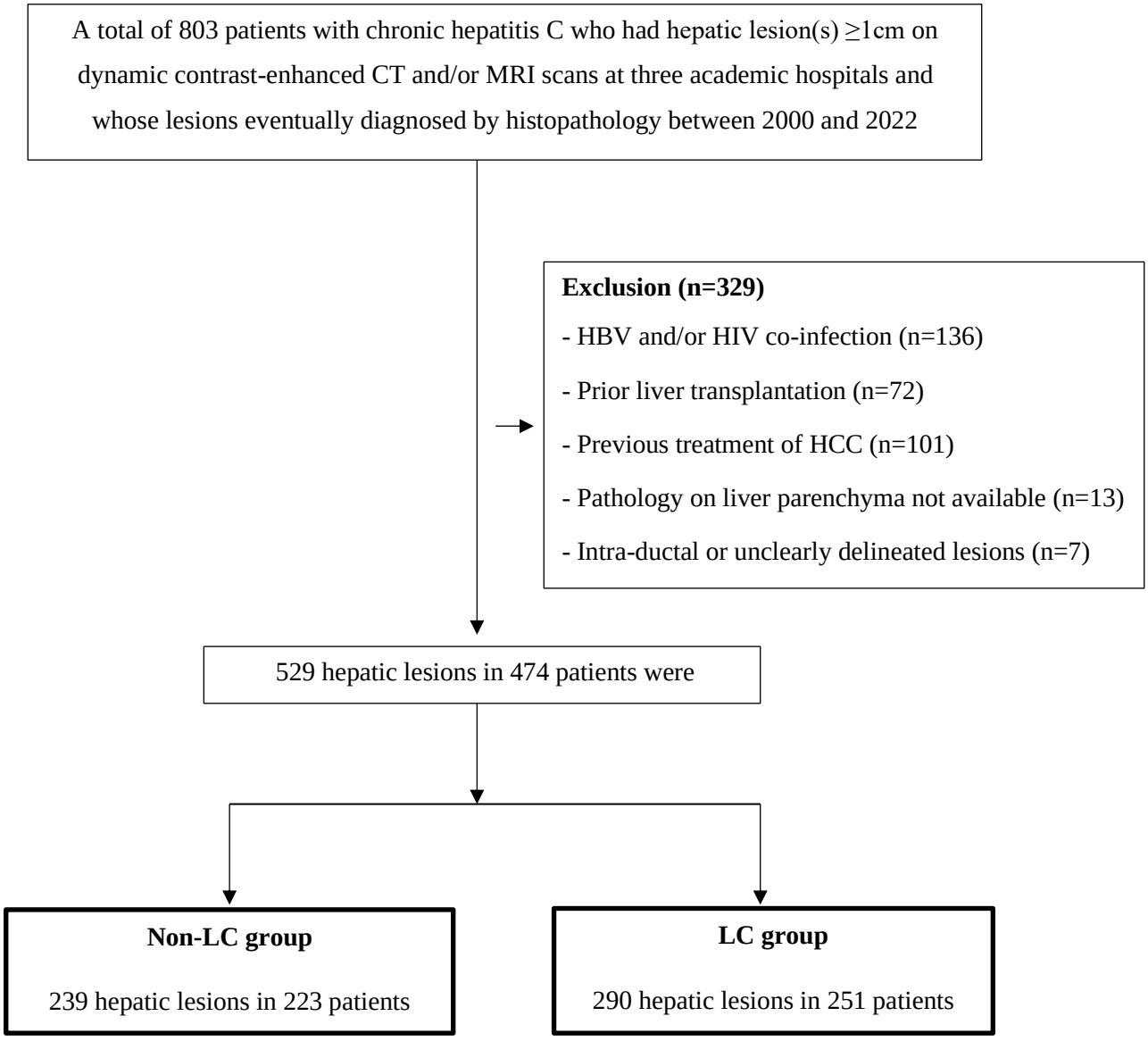
Multicenter Set of Patients

Our initial recruitment efforts targeted a consecutive 803 patients aged 20 years or older who had chronic HCV infection. These patients underwent biopsy or surgical resection for focal liver lesions at three university hospitals in South Korea: Asan Medical Center in Seoul, Hanyang University Guri Hospital, and Jeju University Hospital, between January 2000 and February 2022. Chronic hepatitis C was defined by a positive anti-HCV antibody test and a history of viremia lasting more than 6 months, regardless of any anti-HCV treatment, in line with the European Association for the Study of the Liver (EASL) and AASLD guidelines.[12, 13] If a patient underwent hepatectomy after a biopsy procedure, the final pathologic diagnosis was based on the surgical specimens. Expert pathologists from each hospital reviewed all slides.

Inclusion criteria demanded that patients have at least one hepatic lesion measuring 1 cm or larger, recognized as the minimum threshold for nodule diameter for the non-invasive diagnosis of HCC as per references like LI-RADS, EASL, and AASLD.[7, 8, 14] This lesion should be evident on dynamic contrast-enhanced CT and/or MRI scans taken within the 3 months leading up to the histopathological examination. Exclusions were made for patients with a co-infection of HBV and/or human immunodeficiency virus (n=136), those with a transplanted liver (n=72), any with a history of prior treatment for HCC (n=101), those without histological specimens of liver parenchyma (n=13), and cases with intra-ductal or poorly delineated lesions (n=7). Consequently, 529 hepatic lesions from 474 patients were considered for the final analysis (as detailed in **Figure 1**). Notably, none of these patients had concurrent cholestatic or immune-related liver diseases at the outset of the study.

This retrospective investigation received approvals from the Institutional Review Boards at the three participating institutions, with the respective reference numbers: 2022-0413 for Asan, 2023-08-035 for Hanyang, and 2023-01-007 for Jeju.

Figure 1. Flow diagram of patient enrollment. Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; HBV, hepatitis B virus; HIV, human immunodeficiency virus; HCC, hepatocellular carcinoma; LC, liver cirrhosis.



Diagnostic Definitions of Underlying Liver Status

The presence or absence of LC was histologically verified for all included patients, giving preference to surgical pathology over biopsy. Based on the confirmatory diagnosis, patients were classified into two groups: the non-LC group (n=223) and the LC group (n=251). Regarding hepatic steatosis, it was diagnosed radiologically based on specific criteria from CT or MRI scans: on CT, the liver had a similar or lower density compared to the spleen; on MRI, the liver parenchymal signal intensity showed a signal drop in the out-of-phase images relative to the in-phase images.[15, 16]

Data Collection and Definitions of Key Clinical Indicators

For each patient and lesion, we reviewed and collected demographic and clinical information, laboratory data at the time of the imaging test, and pathology reports from the integrated Electronic Medical Record systems of individual hospitals. Diabetes mellitus was defined by a fasting glucose level of ≥126 mg/dL, a prior diagnosis of diabetes, or treatment with an anti-diabetic agent or insulin.[17] Smoking and drinking status were designated as positive for current behaviors. We also evaluated the risk of liver fibrosis using the aspartate aminotransferase to platelet ratio index (APRI), calculated as: aspartate aminotransferase (AST) (IU/L) divided by the upper limit of normal AST (IU/L) multiplied by 100 and then divided by the platelet count (10^9/L).[18] The APRI score was employed to further classify patients as being at high vs. low risk for advanced fibrosis, with scores >1.5 indicating high risk and scores <1.5 indicating low risk.[6]

Additionally, we utilized the aMAP score to assess the impact of HCC prevalence on LI-RADS designation.[19] The aMAP scores were derived using the following equation: aMAP score = ((0.06 × age + 0.89 × sex (where male is 1 and female is 0) + 0.48 × ((log10(total bilirubin) × 0.66) + (albumin × -0.085)) - 0.01 × platelets) + 7.4) divided by 14.77 × 100, where age is measured in years, total bilirubin in μmol/L, albumin in g/L, and platelets in 10^3/mm^3.

CT and MRI Techniques

All patients underwent multiphase liver CT and/or MRI with all examinations meeting the technical acquisition standards of LI-RADS v2018 [14]. All CT examinations were performed on 64 or 128 channel multidetector CT scanners. After unenhanced images were acquired, 1.5–2 mL/kg of body weight of iodinated contrast material was injected intravenously using a power injector at a rate of 3–4 mL/s. Subsequently, the acquisition of late arterial-phase (determined using a bolus triggering method), portal venous-phase (70–90 seconds), and delayed-phase (3 minutes) images took place.

All MRI examinations were conducted on either a 3.0 T (Magnetom Skyra, Siemens Healthineers) or a 1.5 T (Magnetom Avanto; Siemens Healthineers) scanner. The MRI protocol included unenhanced MRI sequences, T1-weighted dual gradient-echo in- and opposed-phase imaging, respiratory-triggered turbo spin echo T2-weighted imaging, and diffusion-weighted imaging using a respiratory-triggered single-shot echo-planar imaging sequence with b-values of 0, 50, 500, and 900 s/mm^2. For contrast-enhanced MRI, agents such as gadoxetic acid or gadoterate meglumine were used. T1-weighted 3D gradient-echo imaging was performed before and after injection of contrast media, and during the arterial-phase (5 seconds post peak aortic enhancement determined using a 1.0 mL test bolus injection), portal venous-phase (50–60 seconds), transitional-phase (3 minutes), and hepatobiliary-phase (20 minutes).

Image Analysis

All imaging studies were anonymized, randomized, and independently reviewed by two board-certified abdominal radiologists at each institution. The readers were informed about the location, number, and size of the target lesions to be analyzed, but were blinded to any clinical or pathologic results. An investigator, not involved in the imaging analysis, listed the target lesions with reference to pathologic reports. In cases of discrepancies between the readers' interpretations, they re-evaluated the images collaboratively and reached a consensus.

For the imaging characteristics of target lesions, the readers assessed lesion size and determined the presence or absence of major features (such as arterial-phase hyperenhancement, washout, enhancing capsule, and threshold growth) and ancillary features in accordance with LI-RADS v2018.[14] They then assigned a LI-RADS category to each lesion (e.g., LR-3 for intermediate probability of malignancy; LR-4 for probable HCC; LR-5 for definite HCC; LR-TIV for definite tumor-in-vein; LR-M for probable or definite malignancy but not HCC-specific). Only LR-5 was considered as a test-positive for HCC. Additionally, the readers evaluated the imaging characteristics of the background liver with respect to steatotic liver disease. In instances where the LI-RADS categorization differed between CT and MRI, the MRI-based observation was chosen as the final LI-RADS category, given its superior suitability for LI-RADS.[14, 20]

Statistical Analysis

Categorical variables were analyzed using the chi-square test or Fisher's exact test, while continuous variables were assessed using the t-test. To gauge the diagnostic performance of imaging observations in detecting HCC, we calculated accuracy metrics such as sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), area under the curve (AUC), positive likelihood ratio (LR+), and negative likelihood ratio (LR-). The 95% confidence intervals for the AUC values were determined via bootstrapping with 1000 iterations. ROC curves of models were compared using DeLong’s test.[21]

To ascertain the required sample size, we employed the confidence interval method using the exact Clopper-Pearson formula. Assuming an HCC prevalence of 80% within the noncirrhotic target population and based on a specificity of 0.9, a sensitivity of 0.7, and a precision of 0.02, it was estimated that a sample size of 221 lesions would be needed for the group.

We used the aMAP score to assess the influence of pre-test probability on the diagnostic efficacy of imaging criteria. The pre-test probability of HCC was handled as a numerical variable and modeled via logistic regression for each respective score. The study also explored the impact of pre-test probability of HCC on the subsequent post-test probability after applying imaging criteria, with a

particular focus on the LR-5 category. Post-test probabilities of HCC were derived across a range of theoretical pre-test probabilities, spanning from 40% to 90%, using the Fagan nomogram and the likelihood matrix.[22, 23]

All statistical procedures were executed using the R statistical software (version 4.2.1; R Foundation Inc.; http://cran.r-project.org). A threshold of $P < 0.05$ was chosen for statistical significance.

Results

Patient Characteristics

Table 1 provides a summary of the characteristics of the 474 patients diagnosed with chronic hepatitis C. The median age of the patients was 65 years (interquartile range [IQR] 58–71), with the majority (75.7%) being male. The median body mass index (BMI) was 24.2 kg/m^2. Notably, 194 patients (50.0%) were classified as obese, with a BMI of 25 kg/m^2 or greater. Among them, 209 patients (44.1%) reported current alcohol consumption, and 133 (28.1%) reported smoking habits. Interestingly, 194 patients (40.9%) had previously undergone anti-HCV therapy, and of these, a significant 84.3% achieved a sustained virologic response. When tested for the presence of the virus, 295 patients (62.2%) were positive for HCV RNA.

Hepatic nodules were detected through surveillance in 166 patients (35.0%). The diagnostic tools utilized were diverse: CT scans were used for 71 patients (15.0%), MRI for 18 patients (3.8%), and a combination of methods was used for 385 patients (81.2%). It is noteworthy that 428 patients (90.3%) had only one detected lesion. The median diameter of the largest nodules identified in patients was 3.0 cm, with an IQR spanning 2.0–4.5 cm. For histological confirmation of these nodules, surgical specimens were obtained from 437 patients, biopsy specimens from 15, and a combination of both methods was used for 22 patients. Additionally, a third of the patients (33.1%) exhibited elevated serum alpha-fetoprotein (AFP) levels, with values greater than 20 ng/mL.

In our study, 53.0% of the patients had underlying LC. A comparison of the baseline characteristics between the LC (n=251) and non-LC (n=223) groups revealed that the non-LC group had a higher prevalence of male patients (83.9% vs. 68.5%, P<0.001), a lower incidence of serum AFP levels below 20 ng/mL (28.1% vs. 37.5%, P=0.039), and a longer diameter for the largest lesion (3.4 cm [IQR, 2.2–5.5 cm] vs. 2.8 cm [IQR, 2.0–3.9 cm], P<0.001). On the other hand, the LC group showed a significantly higher prevalence of both diabetes mellitus (38.3% vs. 20.2% for LC and non-LC groups respectively, P<0.001) and steatotic liver disease (18.3% vs. 11.2% for LC and non-LC groups respectively, P=0.024).

Table 1. Clinical characteristics of study patients

Characteristic	Entire cohort (n=474)	Non-LC (n=223)	LC (n=251)	*P* value
Demographic variables				
Age, years	65 (58–71)	65 (59–71)	64 (57–71)	0.317
Male sex	359 (75.7%)	187 (83.9%)	172 (68.5%)	<0.001
Body mass index ≥25 kg/m^2	194 (50.0%)	82 (36.8%)	112 (44.6%)	0.101
Current smoking habitus	133 (28.1%)	58 (26.0%)	95 (29.9%)	0.404
Current alcohol consumption	209 (44.1%)	107 (48.0%)	102 (40.16%)	0.130
Diabetes mellitus	141 (29.7%)	45 (20.2%)	96 (38.3%)	<0.001
Imaging and pathology characteristics				
Indication for dynamic imaging test				0.143
Surveillance setting	166 (35.0%)	70 (31.4%)	96 (38.3%)	
Non-surveillance setting	308 (65.0%)	153 (68.6%)	155 (61.7%)	
Type of dynamic imaging test				0.091
CT and MRI*	385 (81.2%)	178 (79.8%)	207 (82.5%)	
CT alone	71 (15.0%)	32 (14.4%)	39 (15.5%)	
MRI alone	18 (3.8%)	13 (5.8%)	5 (2.0%)	
Number of lesions per patient				0.051
Single	428 (90.3%)	207 (92.8%)	221 (88.0%)	
Two	38 (8.0%)	16 (7.2%)	22 (8.8%)	
Three or more	8 (1.7%)	-	8 (3.2%)	
Diameter of largest lesion (cm)	3.0 (2.0–4.5)	3.4 (2.2–5.5)	2.8 (2.0–3.9)	<0.001
Types of specimens in pathologic diagnosis				0.107
Resection	437 (92.2%)	153 (83.2%)	237 (94.4%)	
Biopsy	15 (3.2%)	19 (10.3%)	7 (2.8%)	
Biopsy and resection	22 (4.6%)	12 (6.5%)	7 (2.8%)	
Steatotic liver disease	71 (15.0%)	25 (11.2%)	46 (18.3%)	0.024
APRI score	0.88 (0.45–1.75)	0.52 (0.34–0.90)	1.41 (0.82–2.34)	<0.001
Laboratory variables				
AST, IU/L	49 (29–80)	34 (24–57)	64 (41–89)	<0.001
ALT, IU/L	34 (20–60)	31 (18–50)	41 (23–67)	0.001
Bilirubin, mg/dL	0.9 (0.6–1.3)	0.8 (0.5–1.0)	1.1 (0.7–1.5)	<0.001
INR	1.2 (1.1–1.3)	1.1 (1.1–1.2)	1.2 (1.1–1.3)	<0.001

Albumin, g/dL	3.2 (2.8–3.6)	3.3 (3.0–3.7)	3.1 (2.7–3.5)	0.001
Platelets, 10^9/L	147 (106–188)	166 (137–207)	119 (84–165)	<0.001
AFP, ng/mL[†]	9.0 (3.5–41.7)	5.6 (2.7–27.9)	11.7 (5.0–47.1)	<0.001
AFP ≥ 20 ng/mL[†]	156 (33.1%)	62 (28.1%)	94 (37.5%)	0.039
HCV-related factors				
HCV RNA (+) at detection of lesion	295 (62.2%)	128 (57.4%)	167 (66.5%)	0.051
Previous treatment of HCV[††]				0.749
IFN-based	65 (13.7%)	28 (12.6%)	37 (14.7%)	
DAA-based	129 (27.2%)	60 (26.9%)	69 (27.5%)	
None	280 (59.1%)	135 (60.5%)	145 (57.8%)	

Values are presented as number (%) or median (interquartile range).

*Of the 403 patients who underwent dynamic MRI, 384 (95.3%) received gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced imaging.

[†] AFP values were not available for two patients at the time their lesions were detected.

[††] Among the patients treated for HCV, 84.3% (161 out of 191) achieved a sustained virologic response

Abbreviations: LC, liver cirrhosis; CT, computed tomography; MR, magnetic resonance imaging; APRI, aspartate aminotransferase to platelet ratio index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio; AFP, alpha-fetoprotein; HCV, hepatitis C virus; IFN, interferon; DAA, direct-acting antiviral.

Imaging and Histopathologic Analysis of Hepatic Lesions in Chronic Hepatitis C Patients

A total of 529 lesions from 474 patients underwent pathological assessment. These comprised: HCC (n=448, 84.7%), other malignant lesions excluding HCC (n=54, 19.2%), and benign lesions (n=27, 5.1%). A per-nodule analysis, presented in **Table 2**, revealed that 335 nodules (63.3%) exhibited a typical enhancement pattern for HCC (i.e., LR-5) on CT and/or MRI scans. Of these, 331 (98.8%) were histopathologically confirmed as HCC: 160 (98.7%) in the non-LC group and 171 (97.9%) in the LC group. In the non-LC subset, mean nodule diameters progressively increased from LR-3 to LR-5, a trend that mirrored the LC subset. One hepatic lesion in the non-LC group, classified as LR-5 but not as HCC, was identified as combined hepatocellular-cholangiocarcinoma (cHCC-CCA) with no benign tumors present. In the LC group, however, three LR-5 lesions were diagnosed as cHCC-CCAs (n=2) and cholangiocarcinoma (CCA) (n=1). In the non-LC and LC groups, actual HCCs constituted 46.7% and 57.7% of LR-3 nodules, 68.2% and 87.3% of LR-4 nodules, 16.7% and 22.2% of LR-M nodules, and 72.7% and 88.9% of LR-TIV nodules, respectively. Concerning LR-4 lesions, the non-LC group included non-HCC primary or metastatic malignancies (n=7), whereas the LC group had non-HCC malignancies (n=3) and dysplastic nodules (n=5). In the non-LC group, 11 malignant neoplasms associated with LR-TIV were 8 HCCs, 2 CCAs, and 1 metastatic malignancy. Conversely, the LC group presented 9 LR-TIV nodules, with 8 being HCCs and 1 being a CCA.

Further multivariate analysis indicated that a solitary tumor and larger tumor size (≥2 cm) were significant factors independently linked with HCC meeting the LR-5 criteria across the 474 patients (P<0.05 for multivariate regression), whereas the presence of LC was not (as detailed in **Table 1-1**).

Table 1-1. Clinical characteristics according to the presence of HCC in the non-LC group

Characteristic	HCC (n=183)	Other lesions (n=40)	*P* value
Demographic variables			
Age, years	64 (59–71)	66 (60–73)	0.670
Male sex	161 (88.0%)	26 (65.0%)	0.001
Body mass index ≥25 kg/m^2	71 (38.8%)	11 (27.5%)	0.245
Current smoking habitus	51 (27.9%)	7 (17.5%)	0.248
Current alcohol consumption	95 (51.9%)	12 (30.0%)	0.019
Diabetes mellitus	35 (19.1%)	10 (25.0%)	0.535
Imaging and pathology characteristics			
Indication for dynamic imaging test			0.439
Surveillance setting	60 (32.8%)	10 (25.0%)	
Non-surveillance setting	123 (67.2%)	30 (75.0%)	
Type of dynamic imaging test			0.449
CT and MRI*	147 (80.3%)	31 (77.5%)	
CT alone	27 (14.8%)	5 (12.5%)	
MRI alone	9 (4.9%)	4 (10.0%)	
Number of lesions per patient			>0.999
Single	170 (92.9%)	37 (92.5%)	
Two	13 (7.1%)	3 (7.5%)	
Diameter of largest lesion (cm)	3.5 (2.3–5.5)	3.4 (2.0–5.3)	0.198
Steatotic liver disease	18 (9.8%)	7 (17.5%)	0.265
APRI score	0.52 (0.35–0.93)	0.42 (0.29–0.84)	0.182
Laboratory variables			
AST, IU/L	37 (25–58)	27 (22–52)	0.090
ALT, IU/L	31 (19–50)	23 (16–45)	0.309
Bilirubin, mg/dL	0.8 (0.5–1.0)	0.8 (0.6–1.3)	0.472
INR	1.1 (1.1–1.3)	1.1 (1.1–1.2)	0.545

Albumin, g/dL	3.3 (3.0–3.7)	3.2 (3.0–3.7)	0.653
Platelets, 10^9/L	167 (134–208)	164 (142–201)	0.972
AFP, ng/mL*	6.4 (2.9–59.3)	3.2 (3.0–3.7)	<0.001
AFP ≥20 ng/mL*	59 (32.2%)	3 (7.9%)	0.004
HCV-related factors			
Positive HCV RNA at detection of lesion	108 (59.0%)	20 (50.0%)	0.385
Previous treatment of HCV			0.029
IFN-based	22 (12.0%)	6 (15.0%)	
DAA-based	56 (30.6%)	4 (10.0%)	
None	105 (57.4%)	30 (75.0%)	

Values are presented as number (%) or median (interquartile range).
*AFP values were not available for two patients at the time their lesions were detected.
Abbreviations: LC, liver cirrhosis; CT, computed tomography; MR, magnetic resonance imaging; APRI, aspartate aminotransferase to platelet ratio index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio; AFP, alpha-fetoprotein; HCV, hepatitis C virus; IFN, interferon; DAA, direct-acting antiviral.

Table 2. LI-RADS and histopathologic characteristics of hepatic lesions according to the presence of LC (n=529)

Pathologic diagnosis	Total Lesions	LI-RADS categories									
		Lesions in non-LC (n=239)					Lesions in LC (n=290)				
		LR-3	LR-4	LR-5	LR-M	LR-TIV	LR-3	LR-4	LR-5	LR-M	LR-TIV
Number of lesions	529	15 (6.3%)	22 (9.2%)	161 (67.4%)	30 (12.6%)	11 (4.6%)	26 (9.0%)	63 (21.7%)	174 (60.0%)	18 (6.2%)	9 (3.1%)
Diameter of largest lesion (cm)*	3.0 (2.0–4.2)	1.8 (1.3–2.4)	2.6 (2.0–5.0)	3.2 (2.3–5.5)	3.5 (2.0–5.5)	4.0 (3,2–6.4)	1.4 (1.0–2.0)	2.0 (1.6–3.0)	3.0 (2.0–3.9)	2.6 (2.0–3.4)	5.0 (4.2–7.2)
Hepatocellular carcinoma	**448 (84.7%)**	**7 (46.7%)**	**16 (68.2%)**	**160 (99.4%)**	**5 (16.7%)**	**8 (72.7%)**	**15 (57.7%)**	**55 (87.3%)**	**171 (98.3%)**	**4 (22.2%)**	**8 (88.9%)**
Other malignant lesions	**54 (10.2%)**	**1 (6.6%)**	**7 (31.8%)**	**1 (0.6%)**	**23 (76.6%)**	**3 (27.3%)**	**-**	**3 (4.8%)**	**3 (1.7%)**	**12 (66.7%)**	**1 (11.1%)**
Combined HCC-CCA	14	-	2	1	4	-	-	2	2	3	-
Intrahepatic CCA	22	1	2	-	7	2	-	1	1	7	-
Metastatic cancer	18		3	-	12	1	-	-	-	2	-
Benign lesions	**27 (5.1%)**	**7 (46.7%)**	**-**	**-**	**2 (6.7%)**	**-**	**11 (42.3%)**	**5 (7.9%)**	**-**	**2 (11.1%)**	**-**
Angiomyolipoma	1	-	-	-	1	-	-	-	-	-	-
Inflammatory nodule	2	2	-	-	-	-	-	-	-	-	-
Hepatic cyst	3	3	-	-	-	-	-	-	-	-	-
Eosinophilic granuloma	1	1	-	-	-	-	-	-	-	-	-
Hemangioma	2	1	-	-	1	-	-	-	-	-	-
Dysplastic nodule	13	-	-	-	-	-	8	5	-	-	-
Regenerative nodule	5	-	-	-	-	-	3	-	-	2	-

Values are presented as number (%) or median (interquartile range).

Abbreviations: LI-RADS, Liver-Image-reporting and data system; LC, liver cirrhosis; HCC-CCA, combined hepatocellular-cholangiocarcinoma; CCA, cholangiocarcinoma

When examining characteristics of HCCs in non-cirrhotic livers with HCV infection, we noted a higher male prevalence among HCC patients (88.0% vs. 65.0%, *P*=0.001). Furthermore, serum AFP levels ≥20 ng/mL and a history of anti-HCV therapy, particularly with direct-acting agents, were more prevalent in the HCC group (32.2% vs. 7.9%, *P*=0.004; and 43.6% vs. 25%, *P*=0.029, respectively). No other significant differences were detected. More details can be found in **Table 2-1**. A representative LR-5 HCC case in the non-LC group is illustrated with dynamic CT/MRI images and H&E-stained pathological images in **Figure 2.**

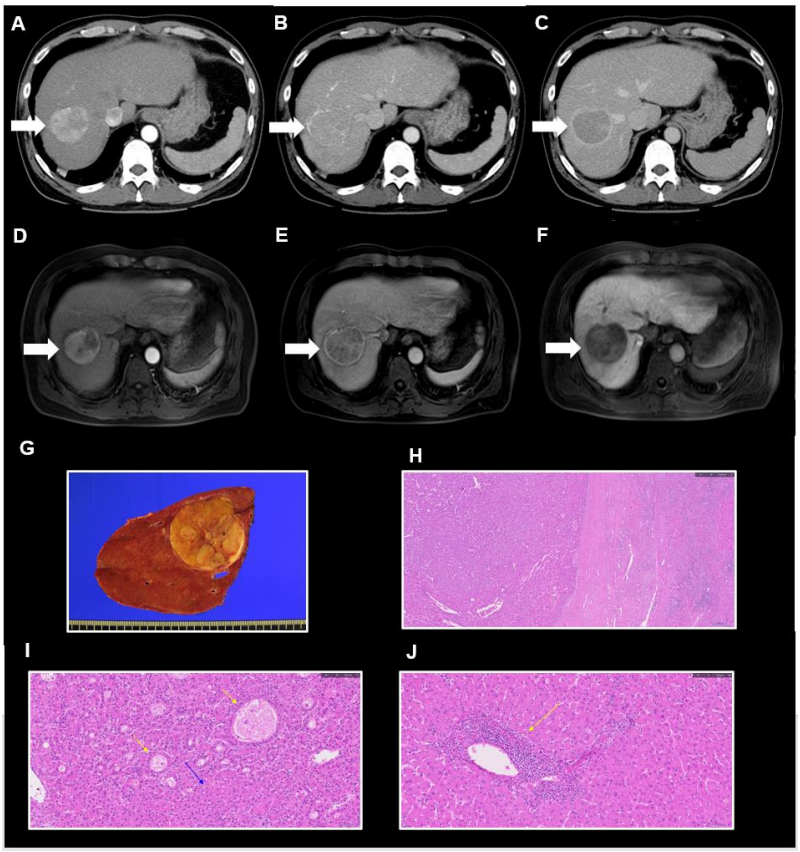
Table 2-1. Demographic and Laboratory Factors Associated with the Likelihood of Having LR-5 HCC in the Entire Cohort (n=474)

Variable	Univariate analysis			Multivariate analysis*		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Age ≥60 years	1.11	0.74–1.68	0.608			
Male sex	1.49	0.96–2.29	0.073	1.27	0.79–2.05	0.330
BMI ≥25 kg/m^2	1.26	0.85–1.86	0.245			
Current smoking habitus	1.11	0.72–1.70	0.639			
Current alcohol consumption	1.53	1.04–2.26	0.032	1.49	0.99–2.23	0.054
Diabetes mellitus	0.70	0.46–1.05	0.086	0.74	0.48–1.14	0.175
Hepatic steatosis	1.17	0.68–2.02	0.566			
Liver cirrhosis	0.80	0.55–1.18	0.265			
AST >40 U/L	1.07	0.73–1.58	0.724			
ALT >40 U/L	1.33	0.90–1.96	0.154			
Platelets <150,000/mm^3	0.61	0.42–0.90	0.014	0.72	0.48–1.08	0.110
AFP ≥20 ng/mL	1.39	0.92–2.11	0.566			
Single tumor	2.10	1.14–3.88	0.017	1.93	1.02–3.65	0.044
Lesion size ≥2 cm	2.92	1.93–4.42	<0.001	2.66	1.74–4.07	<0.001
HCV RNA positivity	1.27	0.87–1.89	0.215			

* Multivariable logistic regression model incorporating all variables with a P-value < 0.1 in the univariate analysis.

Abbreviations: HCC, hepatocellular carcinoma; OR, odd ratio; CI, confidence interval; BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AFP, alpha-fetoprotein; HCV, chronic hepatitis C virus infection

Figure 2. Dynamic images of a representative HCC case alongside its microscopic photographs. This is from a 53-year-old male patient with chronic hepatitis C but without liver cirrhosis. **(A-C)** Multiphase contrast-enhanced CT illustrates a 5.2 cm arterial-phase hyperenhancing mass in segment VII (A) which exhibits washout and an enhancing capsule in the delayed-phase image (C). **(D-F)** Gadoxetic acid-enhanced MRI also reveals arterial-phase hyperenhancement (D), portal venous washout, an enhancing capsule (E), and hepatobiliary-phase hypointensity (F). This mass was categorized as LI-RADS 5 on both CT and MRI and was surgically confirmed as hepatocellular carcinoma. **(G)** Gross photograph of the cut surface of a hepatocellular carcinoma. The tumor is well-circumscribed and round, with no septum formation. The background liver is not cirrhotic. **(H-J)** Representative microscopic photographs of hepatocellular carcinoma. Low power view of tumor (left side) and adjacent background liver (right side) (H&E, x50) (H). High power view of hepatocellular carcinoma (H&E, x200). The tumor cells display a thickened trabecular arrangement (indicated by a blue arrow) and a pseudoglandular arrangement (indicated by a yellow arrow). There is cellular atypia, with observed nuclear membrane irregularity and prominent nucleoli (I). High power view of the adjacent background liver (H&E, x200). The portal tract (indicated by a yellow arrow) displays mild inflammation, but no significant fibrosis is noted (J).



Performance of LI-RADS 5 Imaging Criteria in Diagnosing HCC Among Noncirrhotic HCV-Infected Patients

For all lesions, the LI-RADS 5 criteria demonstrated the following diagnostic capabilities for HCC: sensitivity of 73.9% (95% confidence interval [CI], 69.8–78.0), specificity of 95.1% (95% CI, 90.3–99.8), PPV of 98.8% (95% CI, 97.6–100.0), and NPV of 39.7% (95% CI, 32.8–46.6), as outlined in **Table 3**. For nodules in HCV patients without cirrhosis, the corresponding values were 82.1% (95% CI, 76.7–87.4), 97.7% (95% CI, 93.3–100.0), 99.4% (95% CI, 98.2–100.0), and 55.1% (95% CI, 44.1–66.2). The diagnostic accuracy of the LR-5 observation remained consistent regardless of the presence of LC. However, both sensitivity (82.1% [95% CI, 76.7–87.4] vs. 67.6% [61.8–73.4]) and NPV (55.1% [95% CI, 44.1–66.2] vs. 29.3% [21.0–37.6]) were higher in the noncirrhotic group. Notably, in the noncirrhotic group, the AUC was significantly higher than in the cirrhotic group (0.90 [0.86–0.93] vs. 0.80 [0.75–0.85]; *P* value from DeLong test = 0.002).

Both **Table 3** and **Table 3-1** provide stratified analyses based on various factors, such as age, sex, lesion size, underlying steatotic liver disease, current HCV status, APRI score, serum AFP levels, presence of diabetes mellitus, and the imaging technology used. There were no significant discrepancies in sensitivity and specificity across these subgroups in the non-LC group. Similarly, no significant differences in AUC, PPV, and NPV were observed between the individual subgroups.

Table 3. Performance of LI-RADS 5 criteria for the per-lesion diagnosis of HCC

	Entire nodule (n=529)			Lesions in non-LC (n=239)							
	Total (n=529)	**Non-LC (n=239)**	**LC (n=290)**	**Lesion ≤ 2 cm (n=59)**	**Lesion >2 cm (n=180)**	**With SLD (n=28)**	**Without SLD (n=211)**	**Positive HCV RNA (n=139)**	**Negative HCV RNA (n=100)**	**CT (n=225)**	**MRI (n=207)**
Sensitivity, %	73.9 (69.8–78.0)	82.1 (76.7–87.4)	67.6 (61.8–73.4)	72.1 (58.7–85.5)	84.9 (79.2–90.6)	80.0 (62.5–97.5)	82.3 (76.6–87.9)	81.0 (73.9–88.2)	83.5 (75.4–91.7)	76.3 (70.2–82.5)	81.6 (75.7–87.4)
Specificity, %	95.1 (90.3–99.8)	97.7 (93.3-100.0)	91.9 (83.1–100.0)	100.0	96.4 (89.6–100.0)	87.5 (64.6–100.0)	100.0	100.0	95.2 (86.1–100.0)	92.3 (83.9–100.0)	97.4 (92.5–100.0)
AUC	0.85 (0.82–0.87)	0.90 (0.86–0.93)	0.80 (0.75–0.85)	0.86 (0.79–0.93)	0.91 (0.86–0.94)	0.84 (0.66–0.97)	0.91 (0.88–0.94)	0.90 (0.87–0.94)	0.89 (0.83-0.95)	0.84 (0.79–0.89)	0.89 (0.85–0.93)
LR+	14.96 (11.86–18.88)	36.10 (26.54–49.10)	8.34 (5.86–11.85)	NE*	23.76 (16.18–34.89)	6.40 (2.93–13.97)	NE*	NE*	17.54 (11.17–27.55)	9.92 (7.07–13.93)	31.80 (22.92–44.14)
LR-	0.27 (0.24–0.31)	0.18 (0.16–0.22)	0.35 (0.29–0.42)	0.28 (0.20–0.40)	0.13 (0.05–33.66)	0.23 (0.13–0.40)	0.18 (0.15–0.21)	0.19 (0.15–0.23)	0.17 (0.13–0.22)	0.45 (0.34–0.56)	0.19 (0.16–0.23)
PPV, %	98.8 (97.6–100.0)	99.4 (98.2–100.0)	98.3 (96.4–100)	100.0	99.2 (97.7–100.0)	94.1 (82.9–100.0)	100.0	100.0	98.5 (95.6–100.0)	97.9 (95.6–100.0)	99.3 (97.9–100.0)
NPV, %	39.7 (32.8–46.6)	55.1 (44.1–66.2)	29.3 (21.0–37.6)	57.1 (38.8–75.5)	54.0 (40.2–67.8)	63.6 (35.2–92.1)	53.7 (41.8–65.8)	51.1 (36.5–65.7)	60.6 (43.9–77.3)	45.0 (34.1–55.9)	55.1 (43.3–66.8)

P values by DeLong's test for two ROC curves: LC vs non-LC (*P*=0.002); size ≤2 cm vs. >2 cm (P=0.271); SLD vs. no SLD (*P*=0.356); positive HCV RNA vs. negative HCV RNA (*P*=0.759); CT vs. MR (*P*=0.120).

Abbreviations: HCC, hepatocellular carcinoma; LC, liver cirrhosis; SLD, Steatotic liver disease; CT, computed tomography; MR, magnetic resonance image; HCV, chronic hepatitis C virus; AUC, area under the curve; LR, likelihood ratio; PPV, positive predictive value; NPV, negative predictive value.*LR+ cannot be estimated due to a specificity of 100%.

Table 3-1. Performance of LI-RADS 5 Criteria for Per-Lesion Diagnosis of HCC in the Non-LC Group (n=239)

	APRI <1.5 (n=207)	**APRI ≥1.5 (n=32)**	**Male (n=200)**	**Female (n=39)**	**Age <60 years (n=61)**	**Age ≥60 years (n=211)**	**With DM (n=47)**	**Without DM (n=192)**	**AFP <20 ng/mL (n=172)**	**AFP ≥20 ng/mL (n=65)**
Sensitivity, %	84.1 (78.6–89.6)	68.0 (49.7–86.3)	80.8 (74.9–86.7)	91.3 (79.8–100.0)	81.6 (70.8–92.5)	82. (76.0–88.4)	82.3 (76.3–88.2)	81.1 (68.5–93.7)	83.5 (77.1–89.8)	79.0 (68.9–89.2)
Specificity, %	97.3 (92.1-100.0)	100.0	100.0	93.8 (81.9–100.0)	91.7 (76.0–100.0)	100.0	97.1 (91.4–100.0)	100.0	100.0	66.7 (13.3–100.0)
AUC	0.91 (0.87–0.94)	0.84 (0.74–0.92)	0.90 (0.88–0.93)	0.93 (0.84–1.00)	0.87 (0.76–0.94)	0.91 (0.88–0.94)	0.90 (0.85–0.93)	0.91 (0.84–0.96)	0.92 (0.88–0.95)	0.73 (0.43–0.93)
LR+	31.12 (22.28-43.48)	NE*	NE*	14.61 (8.66–24.65)	9.80 (5.33–18.01)	NE*	27.97 (19.71–39.71)	NE*	NE*	2.37 (0.59–9.55)
LR-	0.16 (0.14–0.19)	0.32 (0.20–0.51)	0.19 (0.16–0.23)	0.09 (0.06–0.15)	0.20 (0.14–0.29)	0.18 (0.15–0.21)	0.18 (0.15-0.22)	0.19 (0.13–0.27)	0.17 (0.14–0.20)	0.31 (0.11–0.87)
PPV, %	99.3 (97.9-100.0)	100.0	100.0	95.5 (86.8–100.0)	97.6 (92.8–100.0)	100.0	99.2 (97.7–100.0)	100.0	100.0	98.0 (94.1–100.0)
NPV, %	57.1 (44.9–69.4)	46.7 (21.4–71.9)	45.9 (33.4–58.4)	88.2 (72.9–100.0)	55.0 (33.2–76.8)	55.2 (42.3–67.4)	54.1 (41.6–66.7)	58.8 (35.4–82.2)	63.9 (51.2–74.9)	13.0 (0–30.5)

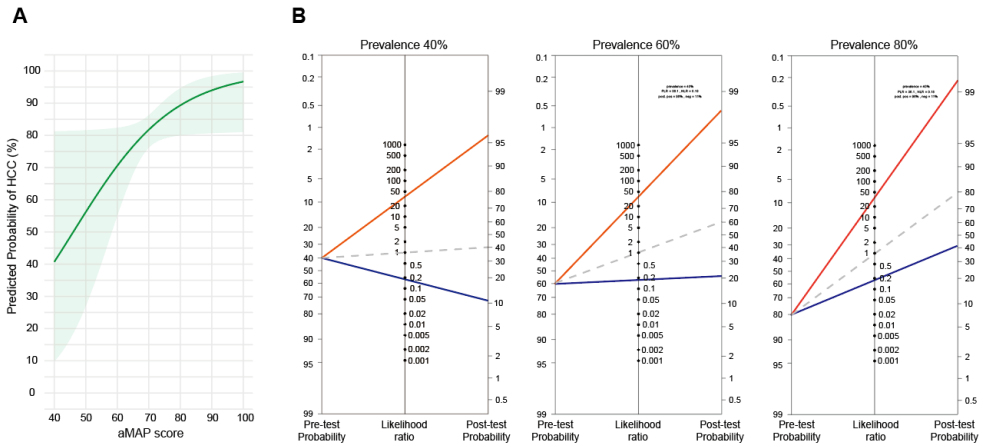
P values by DeLong's test for two ROC curves: APRI <1.5 (low risk of advanced fibrosis) vs. APRI ≥1.5 (high risk of advanced fibrosis) (*P*=0.199); male vs female (*P*=0.646); age <60 years vs. ≥60 years (*P*=0.401); DM vs. no DM (*P*=0.823); AFP <20 ng/ml vs. AFP ≥20 ng/ml (*P*=0.269)

Abbreviations: HCC, hepatocellular carcinoma; LC, liver cirrhosis; APRI, aspartate aminotransferase to platelet ratio index; DM, diabetes; AFP, alpha-fetoprotein; AUC, area under the curve; LR, likelihood ratio; PPV, positive predictive value; NPV, negative predictive value.*LR+ cannot be estimated due to a specificity of 100%

Evaluating Pre-Test and Post-Test Probabilities of LR-5 HCC Based on the aMAP score

Considering our data was gathered from three referral centers and primarily included patients who underwent hepatic resection, there exists a potential bias towards a higher prevalence of true positive LR-5 results. This skewed representation might not mirror routine clinical settings where the prevalence of HCC is comparatively lower. With this in mind, we aimed to gauge the performance of the LI-RADS 5 criteria across different pre-test probabilities for HCC. **Figure 3** showcases a Fagan's nomogram, delineating the shift in pre-test to post-test probabilities of HCC after receiving either positive or negative LR-5 results. In scenarios where the pre-test likelihood of HCC surpasses 80%—as in our study—a positive LR-5 result elevates this post-test probability to a compelling 99%. However, a negative LR-5 outcome reduces this likelihood dramatically to 42%. Such a high pre-test probability (>80%) aligns with a score exceeding 70 on the aMAP scale. This score has been convincingly linked to an elevated risk of HCC among patients with chronic liver diseases, including hepatitis C.[19] Further exploration into how pre-test probability influences the LI-RADS 5 criteria in different HCC prevalence settings revealed interesting insights. For instance, when the pre-test probability stood at 40% or 60%, equating to aMAP scores of 40 and 52 respectively, and the LR-5 criteria were met, the resulting post-test probabilities soared to 96% and 98% in turn

Figure 3. Pre- and post-test probabilities of HCC for LR-5, as estimated by the aMAP score in noncirrhotic patients. (A) Estimation of pre-test probability for HCC based on the aMAP score, utilizing a logistic regression model (logit = −2.87571 + 0.06250 × aMAP). **(B)** Fagan's nomograms used to calculate post-test probabilities of HCC based on LI-RADS 5 criteria, considering theoretical pre-test probabilities of 40%, 60%, and 80% in HCV patients without liver cirrhosis. The orange line indicates the post-test probability if the test is positive, whereas the navy line indicates the post-test probability if the test is negative.



Discussion

Most clinical practice guidelines globally restrict the noninvasive diagnosis of HCC to cirrhotic livers.[8, 14] To date, imaging alone in noncirrhotic HCV livers has not been universally recognized as sufficient for establishing an HCC diagnosis. It's worth noting that liver tumor biopsies, though essential, present potential risks.[24, 25] While instances of bleeding and needle track seeding are relatively rare and typically manageable, the reduced sensitivity of biopsies—particularly for tumors smaller than 2 cm—is an undeniable concern.[26-28]

In our multicenter radio-pathological correlation study, CT/MRI LI-RADS 5 observations demonstrated an impressively high accuracy level, boasting a specificity of 97.7% and a PPV of 99.4% for HCC diagnosis in rigorously defined, histologically-confirmed noncirrhotic patients with chronic HCV infection. These diagnostic efficiencies are on par with those observed in cirrhotic patients. In theory, for a diagnostic test to effectively bypass a biopsy, its PPV and specificity should closely approach 100% to minimize false positives.[29] It's intriguing to consider that LC, irrespective of its cause, is a potential risk factor for non-HCC hepatic malignancies like CCA and combined HCC-CCA.[30-33] In our study, the cirrhotic group surprisingly exhibited a reduced per-observation sensitivity for LR-5 HCCs, with the category including cancers with CCA pathology in 1.7% of cases. Factors such as hepatic steatosis, diabetes mellitus, male gender, higher APRI score, and HCV viremia, which have been linked with an elevated risk of HCC,[6, 34-36] did not influence the diagnostic capability of LR-5 for noncirrhotic HCC. Further analyses revealed that neither a larger nodule size (>2 cm) nor the MRI method—both potential enhancements to LI-RADS imaging sensitivity—affected the outcomes.[20, 26, 37] Conversely, the diagnostic results for LR-5 HCC in our LC cohort were consistent with prior data from cirrhotic populations affected by various diseases.[38-40] This consistency underscores the reliability of our study's performance metrics.

Crucially, it's reported that up to 20% of all HCCs originate in noncirrhotic backgrounds, including those infected with HCV. These often present with typical and non-distinctive histopathologic and radiologic features.[41, 42] Even HCV patients who haven't progressed to LC, or those who have seen LC regression post-antiviral treatment, still exhibit a heightened risk of developing HCC compared to the general population—albeit, the risk is somewhat attenuated compared to individuals with concurrent LC.[5, 6] Given the remarkably high rates of HCV clearance achieved by contemporary antiviral therapies,[1] the ability to accurately and non-invasively diagnose HCC will likely become increasingly critical for cured noncirrhotic patients moving forward. However, the direct oncogenic mechanisms exerted by HCV viral proteins—beyond the progressive effects of chronic liver inflammation—remain elusive.[41, 43]

In our complete cohort, 331 out of the 448 HCCs (73.9%) were classified under the LR-5 category, with 160 (81.2%) observed among the 197 noncirrhotic patients. These figures align with previous findings that assessed typical HCCs based on EASL radiological criteria, notably arterial phase hyperenhancement and either portal venous or delayed washout.[8] The LI-RADS system, which has garnered superior recognition over other imaging criteria and has received endorsement from the AASLD, stipulates that liver nodules falling under LR-3, LR-4, LR-M, or LR-TIV categories (excluding LR-5) should be recommended for biopsy.[14] This recommendation is driven by the perceived insufficient pre-test probabilities of imaging alone in providing a conclusive malignant diagnosis. Uniquely, our study is the inaugural report to validate the performance of the LI-RADS algorithm for diagnosing HCC, specifically focusing on a cohort of noncirrhotic HCV patients. Our study represents the first evaluation of the LI-RADS algorithm's diagnostic efficacy for HCC in noncirrhotic HCV patients, compared to their cirrhotic counterparts of the same Korean ethnicity.

In fact, few studies have explored the diagnostic accuracy of LI-RADS for HCC in patients with chronic HCV but without LC. A non-consecutive study by Ludwig et al., which evaluated the LI-RADS v2018 criteria for the diagnosis of HCC among primary liver cancers of hepatocellular and/or cholangiocellular origin in 131 patients with noncirrhotic disorders—including 6 HCV carriers—reported a high specificity of LR-5 (97-100%).[44] This striking observation might be attributed to the exclusive inclusion of the three types of malignant pathologies without any benign neoplasms. In a recent pivotal cross-sectional study from Mount Sinai Hospital in New York, where LR-5/LR-TIV was taken as diagnostic for HCC, the criteria confirmed HCC with a specificity of 81.5% and a PPV of 93.4% among 338 focal lesions from noncirrhotic HBV livers.[11] The prevalence of HCC nodules in this cohort was 76%. These values were comparable to those from our HCV cohort without LC. Furthermore, it was estimated that a pre-test probability above 70%, equivalent to a PAGE-B score of 10 that can stratify HBV patients by their risk of HCC, would be associated with a post-test probability of HCC greater than 90%. Based on these findings, AASLD no longer requires histologic confirmation for LR-5 hepatic nodules in noncirrhotic HBV patients with a PAGE-B score of >9.[7]

The aMAP score, which includes routine demographic and laboratory parameters such as age, sex, albumin, bilirubin, and platelets, has been validated in multiple cohorts with varying ethnicities and etiologies.[19] Specifically, among a Japanese cohort of 1,077 HCV carriers who underwent antiviral treatment, over 80% had noncirrhotic livers, the C-index value of the score was 0.82. Furthermore, an estimated cut-off value of 60 for the high-risk group yielded a sensitivity of 82.4% and a NPV of 99.2%. These figures were comparable to those observed in Asian or Caucasian HBV cohorts. Another validation study demonstrated that the aMAP HCC model outperformed other competing risk calculators in U.K. cirrhotics with cured HCV.[45] In our analysis of HCV carriers without LC, an aMAP score >70 (indicative of a high risk for HCC) corresponding to a pre-test HCC probability of

>80% might serve as a decisive indicator for the diagnostic use of the LI-RADS 5 criteria. A further extrapolation approach, derived from our series' data for settings with a lower prevalence of HCC nodules, suggests that even a pre-test probability of 40%—estimated by an aMAP score of 40—would be associated with a post-test probability of more than 95%. Therefore, a biopsy might also be avoidable when diagnosing LR-5 HCC in low-risk HCV cases without LC. Indeed, several studies have reported that the probability of LR-5 being indicative of HCC ranges between 95-99% in patients with LC, regardless of etiology.[38-40]

Despite the significant findings presented in this report, our study has certain limitations. Firstly, since patients were recruited from high-volume centers, the prevalence of HCC might be higher than what could be typically expected for HCV patients in a primary care setting. This could further heighten its pre-test probability.[46] Our graphic calculations of the subsequent probabilities of HCC, when combined with the likelihood matrix and the aMAP estimate, could further bolster the reliability of LR-5's performance, especially in clinical settings with a lower pre-test probability. Secondly, the consecutive inclusion of benign masses remains a challenge in retrospective studies like ours, which utilize a pathologic reference standard. However, the diagnosis of LR-1 or LR-2 lesions from imaging can mostly be confirmed without the need for biopsy, as per guidelines (e.g., for simple cysts and hemangiomas).[14, 47] It's important to highlight that relying on pathology-based, rather than clinical reference standards, could introduce a bias when diagnosing LR-2 or LR-3 lesions.[48, 49] This is another contributing factor to the high prevalence of HCC observed in our dataset.

Conclusion

LR-5 demonstrated exemplary performance in diagnosing HCC, boasting a PPV of 99.4% in noncirrhotic patients with persistent or cured HCV infection. This performance is on par with that of cirrhotics, who are already recognized as a high-risk population in the LI-RADS guidelines.[14] Taken together, a noncirrhotic individual with an HCV infection may be considered another indication for the imaging-based diagnosis of LR-5 HCC, even if not at aMAP high-risk.

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국문요약

배경과 목적 : 만성 C 형 간염이 간암 발생의 위험요인으로 알려져 있음에도 불구하고, 간암의 영상학적 진단기준으로 사용되는 LI-RADS 는 간 경변이 동반되지 않은 만성 C 형 간염 환자군에서는 검증되지 않았다. 본 연구에서는 간경화가 없는 환자와 간경화가 있는 만성 C 형 간염 환자군을 비교하여 LR-5 의 간세포암(HCC) 진단 능력을 평가하고자 하였다.

방법 : 국내 3 개의 다 기관에서, CT 또는 MRI 영상검사를 통해 1cm 이상의 간 국소 병변이 확인되고, 병리학적으로 확진된 만성 C 형 간염 환자를 대상으로 데이터를 분석하였다. 모든 영상은 두 명의 영상의학과 전문의가 LI-RADS 분류를 통해 분석하였다.

결과 : 총 474 명의 환자에서 529 개의 병변이 확보되었다. 비 간경화 환자의 경우, 223 명의 환자에서, 239 개의 병변이 확인되었고, 간경화의 환자의 경우, 251 명의 환자에서, 290 개의 병변이 확인되었다. 조직검사 결과, 448 개의 HCC, 54 개의 다른 암종, 27 개의 양성 병변으로 확인되었다. LR-5 로 분류 중, HCC 가 아니였던 병변은 비 간경화 군에서 1 개, 간경화 군에서 3 개가 확인되었다. 비 간경화 군중, LR-5 로 분류된 HCC 진단에 있어서, 민감도 82.1% (95% CI, 76.7-87.4), 특이도 97.7% (93.3-100.0),양성예측률 99.4% (98.2-100.0), 음성예측률 55.1% (44.1-66.2) 로 확인되었다. 비 간경화 군의 특이도와 양성예측도는 간경화군의 특이도 및 양성예측률과 비슷하였다. 계층분석을 통해, HCV 의 바이러스 상태나 영상 종류 등이 LR5 결과에 영향을 미치지 않음을 확인하였다. Fagan’s nomogram 을 이용하여 pre-test prevalence 40% 에 해당되는 aMAP score 40 인 군에서도, LR5 의 HCC probability 가 95% 이상임을 확인하였다.

결론 : 간경화가 없는 만성 C 형 간염환자에서, C 형 바이러스 치료나 aMAP score 에 관계없이 LR-5 분류가 HCC 에 진단에 있어서, 양성예측도 99.4% 로 유용했다. 이러한 결과는 LI-RADS 가이드라인에서 제시하고 입증된 간경화 환자를 대상으로 한 결과와 일치했다. 이번 연구에서 확인된 높은 정확도로 간경화 환자뿐만 아니라 간경화가 없는 만성 C 형간염환자에서도 영상학적 LR-5 분류를 근간으로 한 간암의 진단 가능성을 확인하였다.