https://doi.org/10.3329/cbmj.v15i2.91482

Evaluating the Negative Predictive Value of ACR LI-RADS 5 on Triphasic MRI for Hepatocellular Carcinoma in a Histopathology-Proven Cohort

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Abstract

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality worldwide. The American College of Radiology Liver Imaging Reporting and Data System (ACR LI-RADS) provides standardized criteria for HCC diagnosis on imaging, but the negative predictive value (NPV) of LI-RADS 5 categorization requires validation against histopathology. The objective of the study was to evaluate the negative predictive value of ACR LI-RADS 5 category on triphasic MRI for diagnosing hepatocellular carcinoma using histopathology as the reference standard. This cross-sectional analytic study was conducted from April 2024 to September 2025 in the Department of Radiology & Imaging, BMU. Thirty patients with suspected HCC underwent triphasic MRI and were classified per LI-RADS v2018. Ultrasound-guided biopsies targeted the highest-category observations (LR-4/LR-5). Diagnostic accuracy parameters (sensitivity, specificity, PPV, NPV, likelihood ratios) were calculated using histopathology as the gold standard. Among 30 observations, 16 (53.3%) were categorized as LI-RADS 5 and 14 (46.7%) as LI-RADS 4. Histopathology confirmed HCC in 18 cases (60.0%). The NPV of LI-RADS 5 was 78.6% (11/14), with a sensitivity of 83.3%, specificity of 91.7%, and PPV of 93.8%. The positive and negative likelihood ratios were 10.0 and 0.18, respectively, with an overall accuracy of 86.7% ($p<0.001$). ACR LI-RADS 5 on triphasic MRI shows high specificity (91.7%) and PPV (93.8%) for HCC. The 78.6% NPV suggests LR-5 reliably confirms HCC, though non-LR-5 lesions may still be malignant, necessitating histopathological correlation in equivocal cases.

CBMJ 2026 July: Vol. 15 No. 02 P:213-220

Keywords: Hepatocellular carcinoma, Histopathology, Liver MRI, Negative predictive value, Sensitivity, Specificity

Introduction

Hepatocellular carcinoma (HCC) remains a significant global health challenge, representing the fourth leading cause of cancer-related mortality worldwide and the second most common cause of cancer death in men.[1]. The global burden of HCC continues to rise, with approximately 905,677 new cases and 830,180 deaths annually, demonstrating a mortality-to-incidence ratio that reflects the aggressive nature of this malignancy.[1] Notably, about 75% of liver cancer cases occur in Asian regions, with China bearing the highest absolute number of cases.[1] Cirrhosis, regardless of etiology, is identified in 80-90% of HCC patients, establishing it as the predominant risk factor for hepatocarcinogenesis.[1,2] The etiological landscape of HCC has undergone significant epidemiological shifts in recent years.[2,3] While chronic hepatitis B and C viral infections traditionally accounted for 60-85% of HCC cases globally, there has been a notable transition from virus-related

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liver disease to non-viral etiologies, including alcohol-associated liver disease and metabolic dysfunction-associated steatotic liver disease (MASLD), particularly in Western populations.[2,3] These shifts have important implications for surveillance strategies and diagnostic approaches, especially as the prevalence of obesity and diabetes continues to increase worldwide.[3] The American College of Radiology Liver Imaging Reporting and Data System (LI-RADS) was developed to standardize the interpretation and reporting of liver observations in patients at risk for HCC.[4] Since its introduction, LI-RADS has undergone several revisions, with version 2018 representing a comprehensive update that harmonizes with major international practice guidelines.[4,5] The system categorizes liver observations from LR-1 (definitely benign) to LR-5 (definitely HCC), with LR-M reserved for observations that are malignant but not specific for HCC.[4,6] Major imaging features defining LR-5 include non-rim arterial phase hyperenhancement, non-peripheral washout, and enhancing capsule appearance.[4,5] The diagnostic performance of LI-RADS has been extensively evaluated in systematic reviews and meta-analyses. A comprehensive meta-analysis reported a pooled sensitivity of 80% and specificity of 89% for LI-RADS in HCC diagnosis, with the 2018 version demonstrating the highest sensitivity (83%) among all iterations.[7] However, most validation studies have focused on the positive predictive value of LR-5, with reported PPVs exceeding 95% in many cohorts.[7,8] The negative predictive value (NPV) of LR-5 categorization—essentially, the probability that an observation not classified as LR-5 is indeed non-HCC—has received comparatively less attention in the literature. A comparative study of contrast-enhanced ultrasound and MRI LI-RADS reported NPVs of 70.45% and 68.18%, respectively, for LR-5 Categorization.[8] Similarly, a meta-analysis of LR-M observations found that 29% of lesions categorized as LR-M ultimately proved to be HCC at histopathology, highlighting the diagnostic uncertainty associated with non-LR-5 categorizations.[6] These findings underscore the importance of understanding the negative predictive value of LR-5, as patients with observations not meeting definitive HCC criteria may still harbor malignancy, potentially delaying appropriate treatment. The clinical utility of any diagnostic test depends not only on its ability to rule in disease (positive predictive value) but also on its capacity to rule out disease (negative predictive value). In the context of HCC surveillance and diagnosis, understanding the NPV of LR-5 is crucial for clinical decision-making. A high NPV would provide reassurance that patients without LR-5 observations can be safely monitored without immediate tissue diagnosis, while a lower NPV would mandate a lower threshold for biopsy in indeterminate lesions.[9,10] To date, few studies have specifically evaluated the negative predictive value of ACR LI-RADS 5 on triphasic MRI using histopathology as the reference standard in a prospectively enrolled cohort. This study aims to address this gap by assessing the diagnostic performance of LR-5 categorization, with particular emphasis on its negative predictive value, in patients with clinico-radiological suspicion of HCC undergoing histopathological correlation.

Methodology

This cross-sectional analytic study was conducted from April 2024 to September 2025 in the Department of Radiology & Imaging, BMU. Thirty patients with clinico-pathological and radiological suspicion of hepatocellular carcinoma were enrolled using purposive sampling, accounting for potential data loss.

Inclusion criteria: Patients with focal hepatic lesions and liver cirrhosis, chronic hepatitis B or C infection, current or prior diagnosed HCC, adult liver transplant subjects, transplant liver recipients, or NAFLD/NASH/MASH were included.

Exclusion criteria: Patients with cirrhosis due to congenital hepatic fibrosis or vascular disorders (hereditary hemorrhagic telangiectasia, Budd-Chiari syndrome, chronic portal vein occlusion, cardiac congestion, diffuse nodular regenerative hyperplasia), known primary extrahepatic malignancy, refusal to undergo MRI or biopsy, or unavailable histopathology reports were excluded.

Study procedure: All participants underwent triphasic MRI (SIEMENS MAGNETOM SKYRA 3T) with extracellular contrast. Images were acquired in arterial (15-25s), portal venous (60-80s), and delayed phases (2-5min). Observations were classified per LI-RADS v2018 major features; ancillary features were not considered. Ultrasound-guided biopsy was performed from the highest LI-RADS category observation (LR-4 or LR-5). Specimens underwent routine hematoxylin and eosin staining for histopathological examination.

Data analysis: Sensitivity, specificity, accuracy, predictive values, and likelihood ratios were calculated using histopathology as the reference standard. Fisher's Exact test assessed diagnostic performance. Statistical analysis employed SPSS version 26.0, with $p<0.05$ considered significant.

Results

A total of 30 patients with clinico-radiological suspicion of hepatocellular carcinoma were included in this study. The demographic analysis revealed that hepatocellular carcinoma predominantly affected older individuals, with 43.3% of participants aged between 61 and 80 years (mean age 56.97±14.61 years, range 22-82 years). Males constituted the majority of the study population (86.7%), reflecting the known gender disparity in HCC prevalence (Table: I). Clinically, abdominal pain was the most frequently reported symptom, present in 60.0% of cases, followed by jaundice and palpable mass, each observed in 20.0% of patients (Fig. I). Triphasic MRI findings demonstrated that most observations were larger than 5 cm (50.0%), followed by those measuring 2-5 cm (40.0%). Multiple observations were more common (73.3%) than solitary lesions (26.7%). The right hepatic lobe was the predominant site of involvement (90.0%). On T1-weighted pre-contrast imaging, the majority of observations (63.3%) showed hypointense signal intensity. Arterial phase imaging revealed that 96.7% of observations exhibited non-rim hyperenhancement, a key feature of HCC. Washout analysis showed non-peripheral washout in 46.7% of cases, while 40.0% demonstrated no washout. Enhancing the capsule was identified in 43.3% of observations (Table-II). Based on ACR LI-RADS v2018 criteria, 16 observations (53.3%) were categorized as LR-5 (definitely HCC), while 14 (46.7%) were classified as LR-4 (probably HCC) (Fig. II). Histopathological examination confirmed HCC in 18 cases (60.0%). Other diagnoses included metastasis (16.7%), intrahepatic cholangiocarcinoma (10.0%), adenoma (6.7%), and atypical hemangioma (6.7%). Among 16 LR-5 observations, 15 (93.8%) were confirmed as HCC on histopathology. Among 14 LR-4 observations, only 3 (21.4%) proved to be HCC, while the remainder included metastasis (28.6%), intrahepatic cholangiocarcinoma (21.4%), adenoma (14.3%), and atypical hemangioma (14.3%) (Table-III). The diagnostic performance analysis of ACR LI-RADS 5 on triphasic MRI against histopathology demonstrated a sensitivity of 83.3% and specificity of

91.7%. The positive predictive value was 93.8%, while the negative predictive value was 78.6%. The positive likelihood ratio was 10.0, and the negative likelihood ratio was 0.18, with an overall accuracy of 86.7%. Fisher's Exact test yielded a statistically significant p-value of <0.001 (Table-IV).

Table I: Demographic characteristics of study participants (n=30)

Variable	Category	n	%
Age group (years)	20-40	5	16.7
	41-60	11	36.7
	61-80	13	43.3
	81-82	1	3.3
Mean ± SD	56.97 ± 14.61		
Range	(22 – 82) years		
Sex	Male	26	86.7
	Female	4	13.3

Table II: Triphasic MRI characteristics of hepatic observations

Parameter	Category	n	%
Size of observations	1.1 to < 2 cm	3	10.0
	2 to <5 cm	12	40.0
	5 to 15.5 cm	15	50.0
Number of observations	Single	8	26.7
	Multiple	22	73.3
Site of observations	Right lobe	27	90.0
	Caudate lobe	3	10.0
T1 pre-contrast signal	Hypointense	19	63.3
	Iso to hypointense	6	20.0
	Isointense	5	16.7
Arterial phase enhancement	Non-rim hyperenhancement	29	96.7
	Rim hyperenhancement	1	3.3
Washout pattern	Non-peripheral washout	14	46.7
	Peripheral washout	4	13.3
	No washout	12	40.0
Capsule appearance	Enhancing capsule	13	43.3
	Non-enhancing capsule	2	6.7
	No capsule	15	50.0

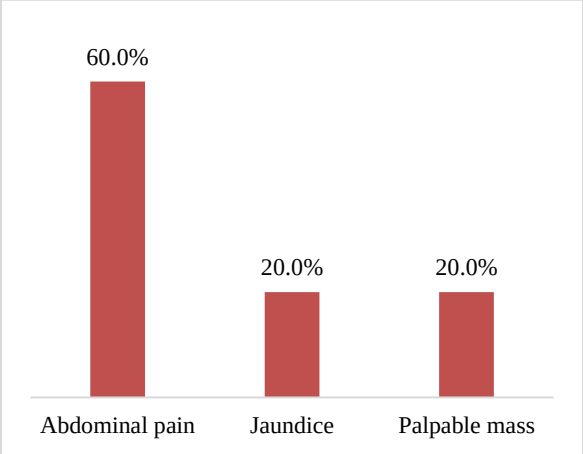

Figure I: Clinical presentations of study participants

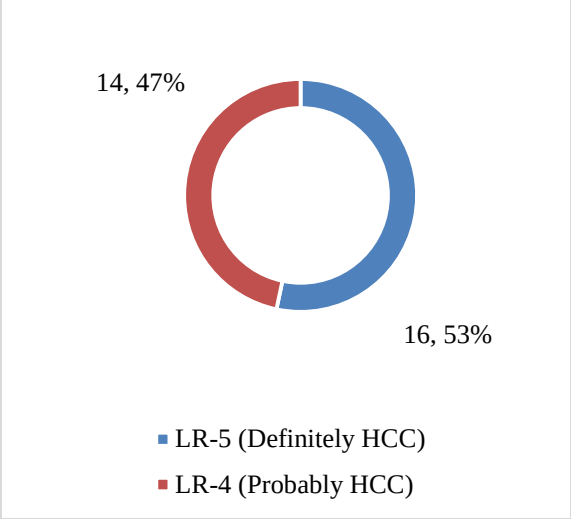

Figure II: Distribution of LI-RADS categories on triphasic MRI

Table III: Histopathological diagnosis compared with LI-RADS category

LI-RADS category	Histopathology results	n	%
LR-5 (n=16)	HCC	15	93.8
	Metastasis	1	6.2
LR-4 (n=14)	HCC	3	21.4
	Metastasis	4	28.6
	Intrahepatic cholangiocarcinoma	3	21.4
	Adenoma	2	14.3
	Atypical hemangioma	2	14.3

Table IV: Diagnostic performance of ACR LI-RADS 5 on triphasic MRI compared with Histopathology

Parameter	Value	95% confidence interval
Sensitivity	83.30%	58.6-96.4%
Specificity	91.70%	61.5-99.8%
Positive predictive value	93.80%	69.8-99.8%
Negative predictive value	78.60%	52.4-92.4%
Positive likelihood ratio	10.0	1.49-67.0
Negative likelihood ratio	0.18	0.06-0.52
Accuracy	86.70%	69.3-96.2%
p-value*	<0.001	

*Fisher's Exact test, p<0.05 considered statistically significant

Discussion

This study evaluated the diagnostic performance of ACR LI-RADS 5 on triphasic MRI for hepatocellular carcinoma, with particular emphasis on its negative predictive value, using histopathology as the reference standard. The findings demonstrate that LR-5 categorization exhibits high specificity (91.7%) and positive predictive value (93.8%) for HCC diagnosis, while the negative predictive value of 78.6% indicates that a substantial proportion of non-LR-5 observations may still represent malignancy. The demographic profile of our study population aligns with established epidemiological patterns of HCC. The mean age of 56.97 years and male predominance (86.7%) are consistent with global literature reporting HCC as a disease predominantly affecting older males.[1,2] The high prevalence of abdominal pain (60.0%) as the presenting symptom reflects the typically advanced stage at diagnosis in resource-limited settings where surveillance programs are not universally implemented.[3] The imaging characteristics observed in our cohort corroborate the major features defined in LI-RADS v2018.[4,5] Non-rim arterial phase hyperenhancement, the cornerstone of LR-5 categorization, was observed in 96.7% of all observations and in all LR-5 cases. This finding is consistent with published literature documenting the high prevalence of arterial hyperenhancement in HCC due to its predominantly arterial blood supply.[7] The washout patterns observed—non-peripheral washout in 46.7% of all observations and 87.5% of LR-5 cases—further support the diagnostic utility of this feature, as it reflects the rapid contrast washout characteristic of HCC.[4,5] The histopathological correlation revealed that 93.8% of LR-5 observations were confirmed as HCC, yielding a PPV of 93.8%. This finding aligns closely with meta-analytic data reporting pooled PPVs exceeding 95% for LR-5.[7,11] The single false-positive LR-5 case in our series was histopathologically proven as metastasis, highlighting that hypervascular metastases can occasionally mimic the imaging features of HCC.[6] This observation underscores the importance of considering clinical context and ancillary features in equivocal cases. The primary focus of this study—the negative predictive value of LR-5—was calculated at 78.6%. This indicates that among observations not classified as LR-5 (i.e., LR-4 in our cohort), approximately one-fifth ultimately proved to be HCC on histopathology. This finding has significant clinical implications, as it suggests that deferring biopsy in all non-LR-5 observations could result in missed HCC diagnoses. Our NPV of 78.6% is comparable to previously reported values of 68-70% in comparative imaging studies.[8,12] The slightly higher NPV in our series may reflect the exclusive use of MRI with extracellular contrast agents and strict adherence to LI-RADS v2018 major features. Among LR-4 observations in our study, only 21.4% were confirmed as HCC, while the majority represented other pathologies, including metastasis

(28.6%), intrahepatic cholangiocarcinoma (21.4%), and benign entities (28.6%). This distribution highlights the diagnostic heterogeneity of indeterminate observations and supports current guidelines recommending tissue confirmation for LR-4 lesions when clinical management would be altered.[4,13] The presence of intrahepatic cholangiocarcinoma among LR-4 observations is particularly noteworthy, as these tumors can exhibit overlapping imaging features with HCC and carry distinct prognostic and therapeutic implications.[6,14] The overall diagnostic accuracy of 86.7% in our study is consistent with published meta-analyses reporting pooled accuracies of 84-88% for LI-RADS.[7,15] The statistically significant p-value (<0.001) from Fisher's Exact test confirms the robust association between LR-5 categorization and histopathological HCC diagnosis. Several limitations of this study warrant consideration. First, the relatively small sample size (n=30) limits the precision of our NPV estimate and precludes subgroup analyses based on observation size or etiology of liver disease. Second, the single-center design may limit generalizability to populations with different demographic or etiological profiles. Third, the exclusion of ancillary features, while methodologically rigorous for assessing major features, may have reduced the sensitivity of LI-RADS categorization in some observations.[16] Fourth, the purposive sampling technique introduces potential selection bias, as patients undergoing biopsy may represent those with more concerning imaging features.[17] Fifth, the exclusive use of extracellular contrast agents, while standard in our setting, may yield different diagnostic performance compared to hepatobiliary-specific agents, which have demonstrated enhanced sensitivity for small HCCs.[18] Despite these limitations, this study provides valuable real-world data on the negative predictive value of LI-RADS 5 in a histopathology-proven cohort. The NPV of 78.6% suggests that while LR-5 is highly specific for HCC, a substantial minority of non-LR-5 observations harbor malignancy, supporting current recommendations for histopathological correlation in indeterminate cases.[4,19] Future research should focus on validating these findings in larger, multicenter cohorts and exploring whether the incorporation of ancillary features or advanced imaging techniques can improve the NPV of LI-RADS categorization. Additionally, cost-effectiveness analyses comparing routine biopsy versus surveillance for LR-4 observations would inform clinical decision-making in diverse healthcare settings.[20]

Limitations

This study has several limitations: small sample size (n=30) limiting precision, single-center design affecting generalizability, exclusion of ancillary features potentially reducing sensitivity, purposive sampling introducing selection bias, and use of extracellular contrast agents only.

Conclusion

ACR LI-RADS 5 on triphasic MRI demonstrates high specificity (91.7%) and PPV (93.8%) for HCC diagnosis, with an NPV of 78.6%. While LR-5 reliably confirms HCC, the moderate NPV indicates that non-LR-5 observations may still harbor malignancy, particularly metastasis and intrahepatic cholangiocarcinoma. Histopathological correlation remains essential for indeterminate lesions to ensure accurate diagnosis and optimal patient management.

Recommendation

Routine histopathological correlation is recommended for LR-4 observations, given the 21.4% prevalence of

HCC. Larger multicenter studies incorporating ancillary features and hepatobiliary agents are needed to improve NPV and validate these findings across diverse populations.

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