Title of the dissertation:

DIAGNOSTIC EFFICACY OF THE LIVER IMAGING-REPORTING AND DATA SYSTEM (LI-RADS) WITH CT IMAGING IN CATEGORISING LIVER LESIONS WITH HISTOPATHOLOGY CORRELATION

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Abstract

Background:

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality globally, particularly among patients with chronic liver disease or cirrhosis. Accurate non-invasive diagnosis of liver lesions is crucial for effective management and treatment. The Liver Imaging Reporting and Data System (LI-RADS), developed by the American College of Radiology, standardizes the classification of hepatic lesions detected in at-risk populations through contrast-enhanced imaging modalities like computed tomography (CT). This study evaluates the diagnostic efficacy of CT-based LI-RADS categorization against histopathological findings in patients with chronic liver disease.

Methods:

This cross-sectional observational study included 45 patients with chronic liver disease or cirrhosis, each presenting with a newly detected hepatic nodule >10 mm on screening ultrasound. All patients underwent multiphasic contrast-enhanced CT, and lesions were categorized using LI-RADS v2018 criteria. Histopathological analysis was performed for all lesions through biopsy or surgical resection, serving as the gold standard for comparison. Diagnostic accuracy metrics—sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall accuracy—were calculated for LI-RADS categories.

Results:

Of the 45 hepatic lesions analyzed, 20 (44%) were categorized as LI-RADS 5, 4 (9%) as LI-RADS 4, 18 (40%) as LI-RADS 3, 2 (4%) as LI-RADS 2, and 1 (2%) as LI-RADS 1. Histopathological evaluation confirmed 29 (64%) as malignant (including 24 HCC and 5 metastases) and 16 (36%) as benign. All LI-RADS 5 lesions were malignant, yielding a specificity and PPV of 100%. Sensitivity for malignancy detection was 69% when using only LI-RADS 5 as a positive indicator. Expanding the threshold to include LI-RADS 4 improved sensitivity to 83%, with maintained specificity of 100% and overall accuracy of 89%.

Conclusion:

CT-based LI-RADS categorization demonstrates high diagnostic specificity and PPV for detecting malignant liver lesions, particularly HCC, in patients with chronic liver disease. Incorporating LI-

RADS 4 as a positive marker for malignancy significantly improves sensitivity without compromising specificity. These findings support the integration of CT LI-RADS into routine surveillance and diagnostic protocols for early and non-invasive detection of HCC, potentially reducing the need for confirmatory biopsies in high-risk populations.

Introduction

Hepatic lesions are frequently encountered in clinical practice and encompass a broad spectrum of benign and malignant pathologies. Accurate characterization of liver lesions is critical for guiding patient management, as it determines the need for further diagnostic work-up or intervention. Imaging plays a central role in this characterization process. In particular, contrast-enhanced computed tomography (CT) is one of the most widely used modalities for evaluating liver lesions due to its broad availability and high spatial resolution.

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver and typically arises in the setting of chronic liver disease or cirrhosis. It is a major health concern worldwide, being a leading cause of cancer-related mortality. Early and accurate diagnosis of HCC is crucial for curative treatment, yet traditionally the definitive diagnosis of malignancy requires histopathological confirmation. However, advancements in imaging techniques and the identification of characteristic imaging features (along with biomarkers like alpha-fetoprotein) now allow HCC to be diagnosed noninvasively in many cases, especially in at-risk patients(1) (2). Both the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) endorse imaging-based diagnostic criteria for HCC in high-risk individuals, obviating the need for biopsy if stringent radiologic criteria are met(2). For instance, a liver nodule >10 mm with arterial-phase hyperenhancement and venous-phase washout on multiphasic imaging can be diagnosed as HCC per established guidelines, given the high positive predictive value of these features (2).

Despite the power of imaging, small lesions (10–20 mm) in cirrhotic livers often pose a diagnostic dilemma. Many such nodules detected during routine ultrasound surveillance may not show the classical hallmark features of HCC on CT or MRI, making it challenging to confidently distinguish early HCC from dysplastic nodules or benign regenerative nodules (1). O'Malley et al. observed that most small (10–20 mm) arterially enhancing nodules in cirrhotic patients did not progress to HCC on follow-up, highlighting that a substantial proportion of these lesions are benign and can be observed safely (1). At the same time, a subset will evolve into malignancy; thus, improved risk stratification of these indeterminate nodules is needed.

Another issue in liver imaging has been the inconsistency in how radiologists interpret and report findings. Historically, individual radiologists might use varied terminology to describe lesion appearance (for example, "indeterminate lesion," "suspicious nodule," etc.), leading to confusion and miscommunication with referring clinicians. The lack of a standardized reporting system introduced variability and errors in patient management decisions. To address these challenges, the

American College of Radiology (ACR) developed the Liver Imaging Reporting and Data System (LI-RADS) – a standardized lexicon and categorization algorithm for liver observations in patients at risk for HCC (3). LI-RADS was first introduced in 2011 and has since undergone several updates (the latest version being LI-RADS v2018) to harmonize with international guidelines and incorporate new evidence (4). The system assigns each hepatic observation a category from LR-1 (definitely benign) to LR-5 (definitely HCC) based on major imaging features on CT or MRI. Additional categories exist for lesions that are probably HCC (LR-4), intermediate probability (LR-3), probably benign (LR-2), as well as LR-M for malignancies other than HCC and LR-TIV for tumor in vein (macrovascular invasion). By standardizing terminology and criteria, LI-RADS aims to reduce inter-observer variability, improve diagnostic accuracy, and facilitate clear communication in a multidisciplinary setting (3).

The LI-RADS framework has been endorsed by liver societies and has been integrated into the AASLD HCC diagnostic algorithm since 2018, aligning imaging criteria across major guidelines (5). The structured approach of LI-RADS not only categorizes the likelihood of HCC but also guides management—for example, an LR-5 lesion in a cirrhotic patient can be treated as HCC without biopsy, whereas an LR-3 indeterminate lesion might warrant closer imaging follow-up or biopsy. Importantly, LI-RADS categorization has implications for transplant eligibility (as part of UNOS criteria in the United States) and for clinical trial enrollment, emphasizing its clinical impact.

Need for the study: Given the advantages of LI-RADS in standardizing HCC diagnosis, it is important to validate its performance on imaging modalities like CT in different clinical settings. Most validation studies of LI-RADS have been done in high-resource settings or using MRI, and data on CT applicability—especially correlating with histopathology as a gold standard—are relatively limited. There is a need to assess how accurately CT-based LI-RADS categorization reflects the true nature of liver lesions, particularly for small lesions detected on surveillance. In patients with cirrhosis under routine HCC surveillance, noninvasive diagnosis is desirable to avoid unnecessary biopsies. However, missing a malignancy at an early stage or misclassifying a benign lesion as HCC can both have serious consequences. Therefore, evaluating the diagnostic efficacy of LI-RADS on CT, by comparing imaging-based categories with histopathological findings, will help determine the reliability of this approach in our patient population.

This study was undertaken to **assess the diagnostic efficacy of LI-RADS with CT imaging in categorizing liver lesions**, with particular focus on small (10–40 mm) nodules in patients at risk for HCC, and to **correlate the LI-RADS categories with histopathological results**. We hypothesize that CT LI-RADS classification has high specificity for HCC (especially for LR-5 lesions) and that using LI-RADS can improve diagnostic confidence, thus potentially reducing unnecessary biopsies for lesions that meet noninvasive criteria for HCC.

Review of Literature

Imaging Diagnosis of HCC in At-Risk Patients

Patients with chronic liver disease, especially those with cirrhosis or chronic hepatitis B, have a high annual risk of developing HCC. For these at-risk populations, regular imaging surveillance is recommended to detect HCC at an early stage when curative treatments are possible. Both AASLD and EASL guidelines call for semi-annual ultrasound screening in cirrhosis, and if a nodule >10 mm is detected, diagnostic imaging with contrast-enhanced CT or MRI is indicated. The noninvasive diagnosis of HCC relies on recognizing a combination of imaging features characteristic of HCC: arterial phase hyperenhancement (APHE) followed by washout in portal venous or delayed phase, and often the presence of a capsule or size >20 mm. When these criteria are met in a high-risk patient, the lesion can be confidently diagnosed as HCC without biopsy (2). This paradigm of imaging-based diagnosis is unique to HCC among solid tumors and stems from the disease's distinct arterial supply and radiologic behavior. It has been validated in studies showing that the positive predictive value of these criteria for HCC is around 95% or higher (2).

Feature	Definition
Nonrim APHE	Nonrim-like enhancement in arterial phase unequivocally greater in whole or in part than the liver. Enhancing part must be higher in attenuation or intensity than the liver in arterial phase
Nonperipheral "washout"	Nonperipheral reduction in the enhancement of lesion from earlier to later phase resulting in hypoenhancement relative to the liver Washout must occur in an extracellular postarterial phase: • For extracellular contrast agents and gadobenate: hypoenhancement in PVP, delayed phase (DP), or both • For gadoxetate: hypoenhancement in PVP only Hypointensity in TP or HBP does not qualify a washout
Enhancing "capsule"	Smooth, uniform, sharp border around most or all of observation, and visible as enhancing rim in PVP, DP, or transitional phase
Threshold growth	Size increase of a mass by $\geq$ 50% in $\leq$ 6 months
Size	Largest outer-edge-to-outer-edge dimension of an observation

"Figure 3. Major LI-RADS imaging features on CT and MRI

(APHE, arterial phase hyperenhancement; CT, computed tomography; DP, delayed phase; HBP, hepatobiliary phase; LI-RADS, Liver

Imaging Reporting and Data System; MRI, magnetic resonance imaging; PVP, portal venous phase; TP, transitional phase.)"

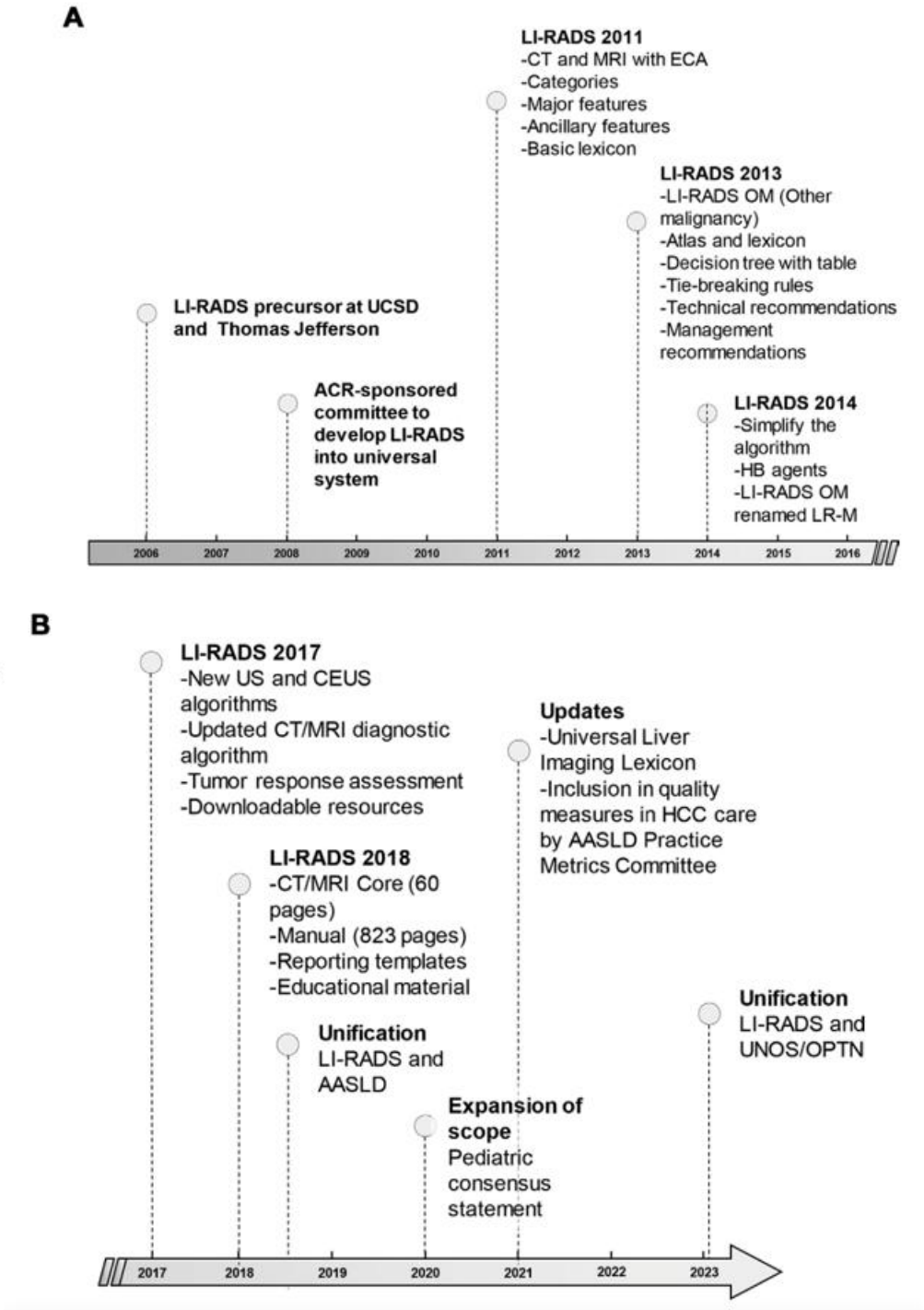
Nevertheless, the sensitivity of the classical imaging criteria decreases for small lesions. Rimola et al. reported that for HCC ≤2 cm, sensitivity of noninvasive criteria is lower, as many early HCCs lack the full complement of hallmarks (for instance, some small HCCs may not exhibit clear washout)(2) (6). In cirrhotic patients, nodules in the 10–20 mm range are frequently encountered; many represent low-grade dysplastic nodules or regenerating nodules rather than frank HCC. As noted, O'Malley and colleagues in a seminal longitudinal study found that 72% of 10–20 mm APHE nodules remained stable or regressed on follow-up and were not HCC, whereas the minority that enlarged were treated as HCC(7). This underscores that while the presence of APHE raises suspicion, it is not definitive on its own for small lesions. The challenge lies in distinguishing those that are truly early HCC from those that are benign. The concept of **"indeterminate" nodules** arose to describe lesions that do not meet full criteria but also are not definitively benign.

Development of LI-RADS and Its Rationale

The Liver Imaging Reporting and Data System (LI-RADS) was created to standardize the interpretation of liver imaging in patients at risk for HCC, addressing the aforementioned challenges of inter-observer variability and ambiguous reporting. Prior to LI-RADS, terms like "probably HCC" or "cannot exclude HCC" meant different things to different readers. LI-RADS introduced a categorical system with defined criteria for each category (LR-1 through LR-5, plus LR-M and LR-TIV). An LR-1 lesion is definitively benign (e.g., a cyst or hemangioma with classic features), while LR-2 is probably benign. LR-3 denotes an intermediate probability of HCC – typically applied to observations that have some concerning features but not enough to be categorized as HCC. LR-4 indicates a probable HCC (not 100% certain, but high likelihood), and LR-5 indicates a definitive HCC by imaging criteria. LR-M is reserved for lesions that have imaging features suggestive of a malignancy that is not a typical HCC (for example, intrahepatic cholangiocarcinoma or metastasis often lack APHE with washout but may have other malignant traits like marked diffusion restriction or peripheral enhancement). LR-TIV (tumor in vein) is used when there is unequivocal radiologic evidence of macrovascular invasion, automatically signifying malignancy (usually HCC) regardless of the primary lesion's appearance.

Each LI-RADS category has an associated implied probability of HCC. By definition, LR-5 lesions are virtually certain to be HCC (≥95% probability) (8). This has been borne out in multiple studies. For example, Liu *et al.* analyzed 297 liver observations with pathology correlation and found that 151 of 156 LR-5 lesions (96.8%) were HCC (8). Similarly, a meta-analysis by Lee *et al.* (2020) reported a pooled specificity of about 94% for LR-5 on CT/MRI, with an extremely high positive predictive value (PPV) for HCC. These results validate that an LR-5 categorization can be

considered diagnostic of HCC in at-risk patients – a fact that has influenced policy, such as allowing LR-5 lesions to be used for UNOS transplant listing without biopsy.



“Figure 4. Timelines summarize major achievements of the Liver Imaging Reporting and Data System (LI-RADS) (A) 2011–2016 and (B) 2017–2023.”

Beyond just identifying HCC, LI-RADS aims to improve communication. A standardized report using LI-RADS categories conveys a clear level of concern. For instance, categorizing a 15 mm nodule as LR-3 (intermediate probability) signals to the clinician that the lesion is indeterminate and typically would prompt either a repeated scan in a short interval or consideration of a second imaging modality, rather than immediate treatment. In contrast, LR-5 would prompt HCC-specific therapy or transplant evaluation, and LR-1/2 would suggest no intervention for that lesion. This structured approach reduces the chance that a significant observation is overlooked or misinterpreted. Becker *et al.* demonstrated that using LI-RADS can increase inter-reader agreement among radiologists and improve diagnostic confidence. In their study, applying an adapted LI-RADS algorithm led to more consistent diagnoses of HCC between different readers compared to free-form assessments.

Step 1	Untreated observation detected
Step 2	LI-RADS category can be applied (Inclusion and exclusion criteria)
Step 3	Technically optimal study (CT/MRI)
Step 4	Apply LI-RADS algorithm for categorization
Step 5	Optional: Apply ancillary features to downgrade or upgrade
Step 6	Optional: Apply tie-breaking rules
Step 7	Final check

“Figure 5. Stepwise approach to CT/MRI LI-RADS diagnosis of nontreated observation”

Importantly, LI-RADS has been updated in tandem with evolving evidence. The 2017 version introduced major changes, and the 2018 version further aligned LI-RADS with the HCC criteria of the Organ Procurement and Transplantation Network (OPTN) and AASLDfile-rpm6ep5tzd1qygzafyuov5file-rpm6ep5tzd1qygzafyuov5. One key principle of LI-RADS (and modern HCC imaging guidelines) is that **specificity is prioritized over sensitivity**. The criteria

for LR-5 are intentionally strict to minimize false positives – virtually no benign lesion should meet LR-5. This means not all HCCs will meet LR-5 (some small or atypical HCCs will be LR-4 or even LR-3), but those lesions that do get an LR-5 designation can be trusted as HCC. The trade-off is that sensitivity is moderate. For instance, in Liu et al.'s study, while LR-5 had near-perfect specificity, a number of HCCs were categorized in lower LR categories (e.g., 3 of 35 LR-3 lesions were actually HCC on pathology)(8) . Therefore, researchers have considered combining categories to improve sensitivity – an approach we will discuss shortly.

Prior Studies on CT LI-RADS Performance

Initial validation studies of LI-RADS often included both CT and MRI or were MRI-heavy, given MRI's higher sensitivity for liver lesions. However, CT remains the workhorse in many centers for HCC diagnosis due to faster acquisition and fewer contraindications. Abd Alkhalik Basha *et al.* (2017) conducted one of the early studies focusing specifically on CT LI-RADS in small (10–20 mm) nodules detected by ultrasound screening(9). In 55 cirrhotic patients with 10–20 mm nodules, they found that 96% of lesions categorized as LR-5 on CT were proven HCC (22/23 lesions) and only one LR-5 lesion (4%) was a false-positive (it was actually a metastasis) (9). No LR-1 lesions were HCC (0/4), confirming that LR-1 indeed represented benign findings. Notably, Basha et al. reported that a substantial proportion of lesions in the "indeterminate" range turned out to be HCC on biopsy: 50% of LR-3 lesions (7 of 14) were HCC, and even 22% of LR-2 lesions (2 of 9) were HCC (9). This highlights that while higher LR categories are very specific, some HCCs will present without all the hallmark features, thus appearing as LR-3 or even LR-2. Basha and colleagues suggested that using a threshold of "LR-4 or LR-5" to define a positive test for HCC significantly increases sensitivity (to ~73%) while maintaining good specificity (~90%) (9). In their data, combining LR-4 and LR-5 as "positive" would have correctly identified a few extra HCCs (those that were LR-4) at the cost of a slight decrease in specificity, since LR-4 lesions can occasionally be false positives.

Another important study by Ronot *et al.* compared LI-RADS (2014 version) head-to-head with earlier AASLD criteria for nodules <3 cm in a prospective cohort (2). On MRI, they found that 94% of LR-5 nodules and ~53% of LR-4 nodules were HCC, whereas on CT 91% of LR-5 and ~55% of LR-4 were HCC (2). These numbers are very much in line with our expectations and with Basha's CT-specific study. Ronot et al. concluded that the LI-RADS algorithm did not significantly outperform the traditional AASLD criteria in terms of overall accuracy for small HCC, primarily because the increased sensitivity by LI-RADS (when counting LR-4 as positive) was offset by some loss of specificity (10). However, LI-RADS provided a more granular classification, especially by identifying those LR-4 "probable HCC" lesions that AASLD would lump together with LR-5 as just "imaging-diagnosed HCC." This granularity can be useful in practice to flag lesions that might need further evaluation.

Choi *et al.* investigated indeterminate (LI-RADS 3) observations and their outcomes on MRI. Their findings showed that the vast majority of lesions without APHE (non-hyperenhancing

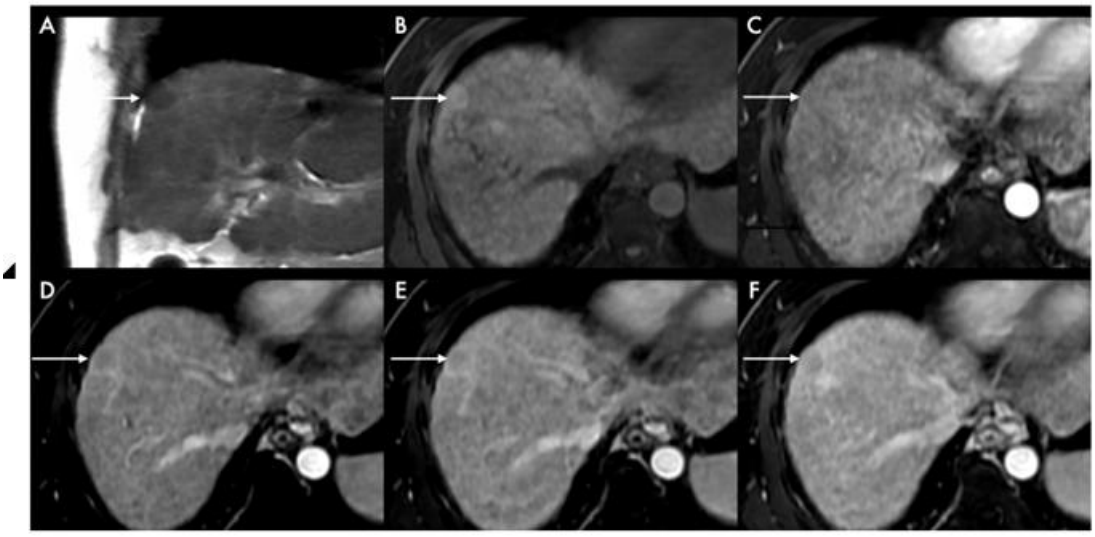
observations) in at-risk patients remained benign on follow-up (11). In one series, only about **one out of 23 non-enhancing nodules (≈4%) eventually proved to be HCC**, meaning the absence of arterial enhancement is highly predictive of a benign lesion in the cirrhotic liver (11). This underscores APHE as a critical feature for HCC diagnosis – its presence triggers consideration of LR-4 or LR-5 if other features align, whereas its absence generally relegates lesions to LR-3 or lower. In the same context, Park *et al.* noted that if one counts LR-4 lesions as "HCC-positive" alongside LR-5, the sensitivity of CT/MRI for HCC improves markedly (into the 70–80% range) with only a modest drop in specificity. They reported that combining LR-4 and LR-5 yielded a sensitivity of ~75% and specificity of ~91%, compared to using LR-5 alone which had higher specificity (~95%) but lower sensitivity. These data have encouraged the practice in some centers of treating LR-4 lesions proactively, or at least investigating them aggressively, since a significant fraction are true HCC.

Apart from adult populations, LI-RADS has been tested in special scenarios. Khanna *et al.* evaluated LI-RADS v2018 for pediatric HCC, which is rare but does occur in children with certain predispositions. They found the system to have **moderate sensitivity but low specificity in children**, as pediatric HCC often does not exhibit typical radiologic features seen in adults (12). In their multi-center study, sensitivity of LR-4/5 for malignancy in at-risk children was only 58–68%, and specificity for benign lesions was 56–63% (12). Many pediatric HCCs lacked the classic imaging hallmarks, reducing LI-RADS accuracy in that context. This highlights that LI-RADS is specifically designed and validated for adult, cirrhosis-related HCC – its performance may differ in other liver tumor types or patient populations.

Another extension of LI-RADS is the Treatment Response algorithm (LI-RADS – LR-TR) for evaluating HCCs after locoregional therapy. While not the focus of our study, it is worth noting a study by Shropshire *et al.* which validated the LR-TR categories against pathology in transplant explants (13) . They found that the LR-TR Viable category (enhancing tissue in treated tumors) had a PPV of 86–96% for residual cancer, whereas LR-TR Nonviable had an NPV of ~81–87% for absence of tumor (13). Inter-reader agreement for LR-TR was moderate ($\kappa \approx 0.55$) (13). This indicates that even in the post-treatment setting, a standardized system like LI-RADS can reliably stratify lesions, reinforcing the broader applicability of the LI-RADS concept to different stages of HCC management.

In summary, the literature suggests that CT-based LI-RADS categorization is highly specific for diagnosing HCC, particularly for LR-5 lesions which have a near-perfect PPV for HCC (8). LR-4 lesions, while not definitively HCC by criteria, represent probable HCC and many will prove to be malignant on histology (9). Combining LR-4 and LR-5 as a positive test substantially improves sensitivity (often into the 80%+ range) with an acceptable trade-off in specificity (9). Lower categories (LR-3, LR-2) encompass a mix of benign and malignant etiologies and thus have limited standalone diagnostic value, but they highlight the subset of lesions where further diagnostic steps (additional imaging, biopsy, or follow-up) are needed. Given these insights, our study will add to the existing evidence by specifically evaluating how well the LI-RADS categories on CT predict

histopathology in our cohort, and by calculating the diagnostic performance metrics (sensitivity, specificity, PPV, NPV, accuracy) for CT LI-RADS in differentiating benign from malignant liver lesions.

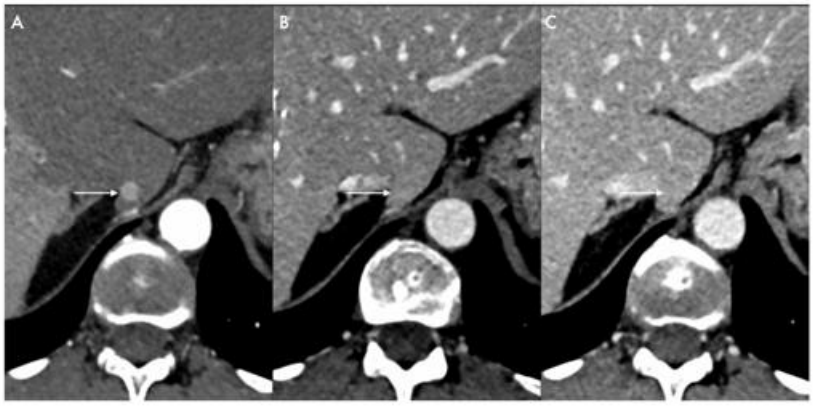


"Figure 6. (A–F) LR-2 observation: A 8 mm focal observation (white arrow) is seen in the subcapsular location of segment VIII, appearing

hypointense on single short fast spin echo coronal images and mildly hyperintense on precontrast T1-weighted images. Observation shows no

definitive enhancement on dynamic postcontrast images."

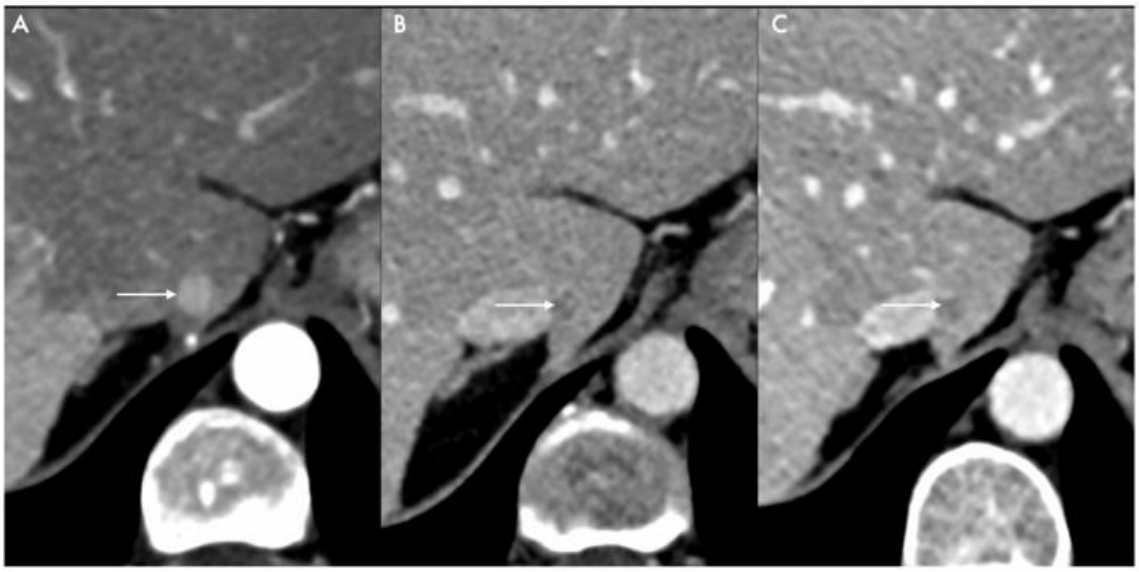
<u>LR-3 category</u>



"Figure 7. (A–C) LR-3 observation: Contrast-enhanced computed tomography study shows a 5 mm observation (white arrow) in segment I showing non-rim arterial phase

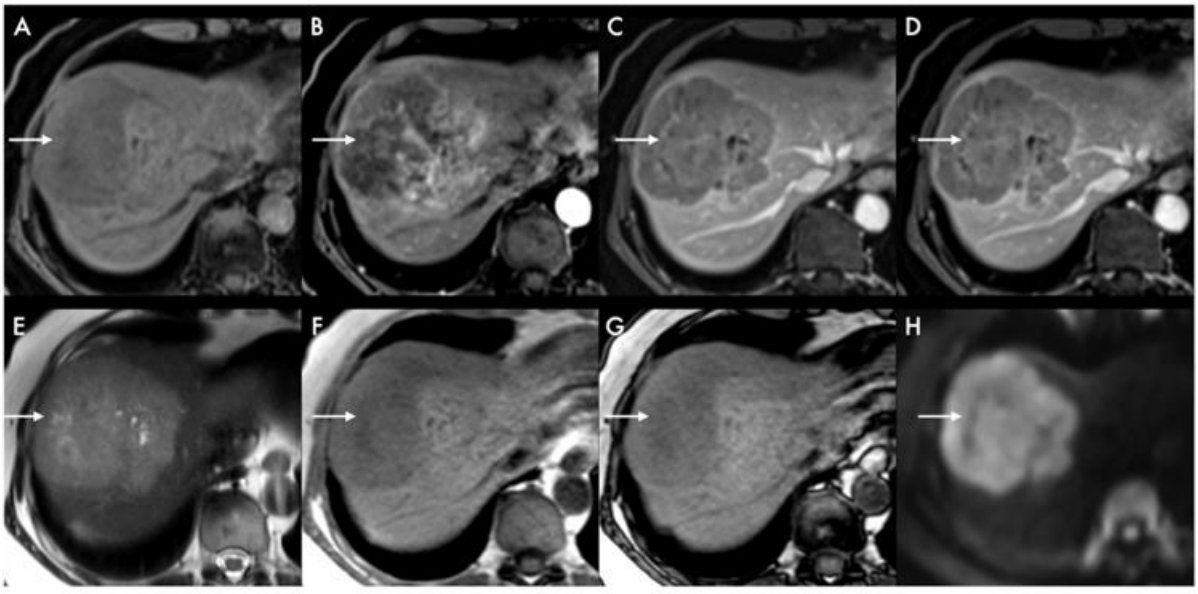
hyperenhancement in late arterial phase (A), without showing washout in portal venous phase (B) or enhancing capsule in delayed phase (C).”

LR-4 category



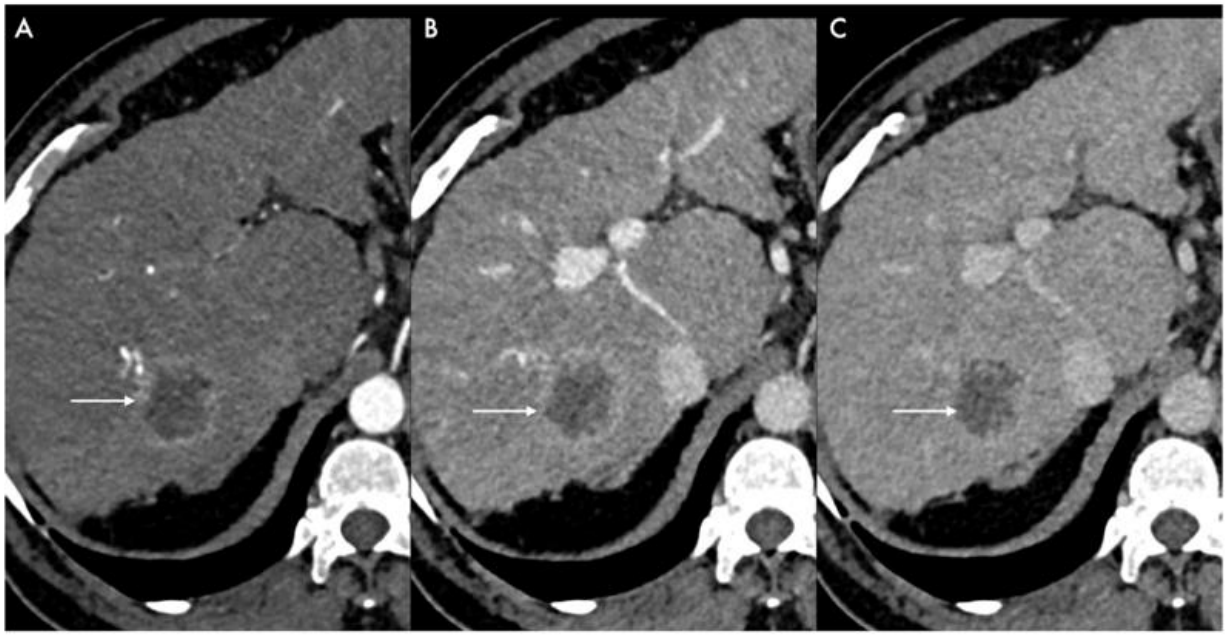
“Figure 8. (A–C) LR-4 observation: Contrast-enhanced computed tomography study shows a 9 mm observation (white arrow) showing nonrim arterial phase hyperenhancement in late arterial phase (A), with nonperipheral washout in portal venous phase (B) and delayed phase (C) without any enhancing capsule in delayed phase (C).”

LR-5 category



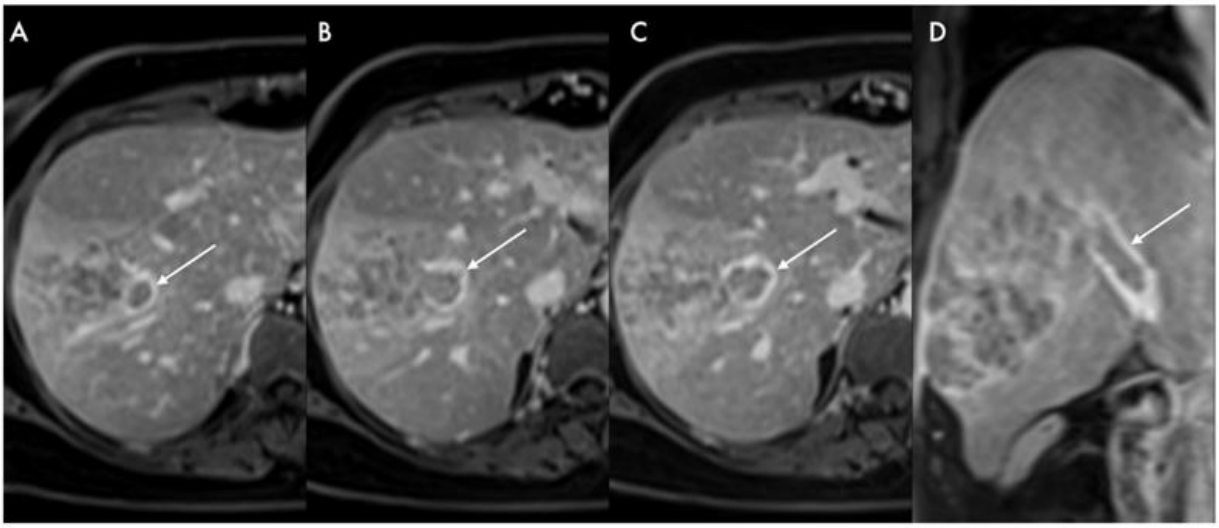
“Figure 9. (A–C) LR-5 observation: Magnetic resonance imaging (MRI) showing the major imaging features of LI-RADS: Contrast-enhanced MRI study shows a 70 mm observation (white arrow) appearing hypointense on T1-weighted (T1W) images (A), showing heterogenous arterial phase hyperenhancement on arterial phase images (B) with washout on portal venous phase images (C) and delayed enhancing rim on delayed phase images (D). Observation appears hyperintense on T2W images (E) showing diffusion-weighted imaging hyperintensity (H), and does not contain fat in phase and out of phase (F, G).”

<u>Category LR-M</u>



“Figure 10. (A–C) LR-M observation: Contrast-enhanced computed tomography study shows a 32 mm observation (white arrow) in segment VII showing rim arterial phase hyperenhancement in late arterial phase (A) and portal venous phase (B) with peripheral washout in delayed phase (C)”.

<u>LR-TIV</u>



"Figure 11. (A–D) LR-TIV: Magnetic resonance imaging venous phase axial (A–C) and coronal images (D) showing a large heterogeneously enhancing lesion in segment VIII (arrow) with definite enhancing soft tissue seen contiguously infiltrating into anterior branch of right portal vein and right portal vein consistent with tumor in vein (TIV)".

Materials and Methods

Study Design and Patients

This study was a cross-sectional observational analysis conducted at Sri Devaraja URS Medical College. The study period spanned 18 months, from November 2022 to April 2024. We included patients with chronic liver disease or cirrhosis who were referred to the Department of Radio-Diagnosis for evaluation of newly detected liver nodules. All patients were adults (age >18 years) under surveillance for HCC due to underlying cirrhosis (of any etiology) or chronic hepatitis B infection. Inclusion criteria were: (1) patients with known cirrhosis or chronic liver disease, **and** (2) detection of a new solitary hepatic nodule >10 mm on screening ultrasound. Patients meeting these criteria were prospectively enrolled after obtaining written informed consent. Exclusion criteria were: patients who **refused biopsy** or did not undergo definitive histological diagnosis of the lesion; patients who had already started treatment for HCC (e.g., transarterial chemoembolization or systemic therapy) prior to imaging; cases with non-diagnostic or indeterminate histopathology results; and patients whose CT scans were nondiagnostic due to severe motion or artifact.

A total of 45 patients met the criteria and were included in the study. The study protocol was approved by the institutional ethics committee, and all procedures were in accordance with the Declaration of Helsinki. Patient confidentiality was maintained, and all data were de-identified for analysis.

Imaging Technique and LI-RADS Classification

All patients underwent multiphasic contrast-enhanced CT imaging of the liver. Scans were performed on a 128-slice multidetector CT scanner (Siemens Healthcare) with intravenous injection of iodinated contrast (approximately 1.5 mL/kg, up to 120 mL, at 3–4 mL/s). Standard triphasic liver protocol was used, including arterial phase (timed by bolus tracking in the abdominal aorta, typically ~20–30 seconds after injection), portal venous phase (~70 seconds), and delayed phase (~180 seconds). Slice thickness for reconstruction was 5 mm (with 1–2 mm thin slices for detailed evaluation when needed).

The CT images were reviewed by two experienced radiologists who were aware that patients were at risk for HCC but were **blinded to the clinical and laboratory details** beyond that (they did not know the specific etiology of cirrhosis or tumor marker levels, and they were blinded to histopathology results). The radiologists independently assessed each lesion and assigned a LI-RADS category (v2018 criteria) based on CT findings. In cases of initial disagreement, the images were reviewed in a consensus meeting to assign a final category. LI-RADS categorization was done according to ACR definitions: evaluating for major features including arterial phase hyperenhancement, washout appearance in portal/delayed phase, capsule appearance, lesion size, and ancillary features if applicablefile-rpm6ep5tzd1qygzafyuov5. No specific LI-RADS calculation software was used; decisions were made manually following the lexicon. By LI-RADS definitions, categories LR-1 through LR-5 were assigned when appropriate. Additionally, observations that exhibited imaging features suggestive of a non-HCC malignancy (such as targetoid appearance or marked central necrosis atypical for HCC) would be labeled as LR-M, and any observation with definite gross venous invasion as LR-TIV. In our cohort, however, all lesions were intrahepatic and none demonstrated frank vascular invasion on imaging; also, none had distinct “targetoid” features to be categorized as LR-M. Thus, all lesions were ultimately given an LI-RADS score in the 1–5 range.

After imaging, all patients underwent histopathological confirmation of the lesion, which served as the reference standard. In most cases (40/45), an ultrasound-guided percutaneous core needle biopsy of the lesion was performed within a few weeks of the CT scan. In a minority of patients (5/45), surgical resection of the lesion was done (due to high clinical suspicion of malignancy or patient preference), and the resected specimen provided the histopathology. An experienced pathologist, blinded to the LI-RADS category, examined the specimens. The histopathological diagnosis was recorded as HCC, benign lesion (with specific subtype such as regenerative nodule or adenoma), or other malignant tumor (e.g., metastasis or intrahepatic cholangiocarcinoma), as appropriate.

Data Collection and Analysis

Patient demographic details (age, sex) and clinical background (risk factors for liver disease, liver function tests) were recorded from medical records. The size of each lesion on imaging was

documented. The primary outcome of interest was the concordance between the LI-RADS category on CT and the histopathological diagnosis (benign vs. malignant, and specific diagnosis). We tabulated the distribution of lesions by LI-RADS category and by pathology result.

For statistical analysis, data were entered into a Microsoft Excel spreadsheet and analyzed using SPSS version 22 (IBM Corp). We used descriptive statistics to summarize the findings. Categorical variables (e.g., distribution of LI-RADS categories, pathology results) are presented as frequencies and percentages. Continuous variables (such as age) are reported as mean ± standard deviation.

We assessed the **association between LI-RADS category and histopathological outcome** (benign or malignant) using the Chi-square test. Specifically, we examined whether higher LI-RADS categories were significantly associated with lesions being malignant on biopsy. A p-value <0.05 was considered statistically significant for this association.

We also evaluated the **diagnostic performance** of LI-RADS on CT for detecting malignancy. Two diagnostic thresholds were analyzed: (1) using **LR-5 alone as a positive test** (i.e., considering only LR-5 lesions as "test-positive" for HCC) and (2) using **LR-4 or LR-5 as a positive test** (i.e., considering both categories 4 and 5 as imaging-positive for malignancy). For each scenario, we constructed 2×2 contingency tables comparing the imaging test (positive/negative) against the gold standard (malignant or benign on histology). From these, we calculated sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall accuracy, along with 95% confidence intervals for these metrics. Sensitivity was defined as the proportion of true malignant lesions correctly identified by the test, and specificity as the proportion of true benign lesions correctly identified. PPV was the probability that an imaging-positive lesion was truly malignant, and NPV the probability that an imaging-negative lesion was benign. Accuracy was the proportion of all cases correctly classified by imaging. The Wilson score method was used to calculate confidence intervals for proportions.

No interim analyses were performed. Given the observational nature of the study, no formal sample size calculation was done; we aimed to include as many eligible patients as possible during the study period. The sample size (45 lesions) is similar to or larger than some prior single-center studies on CT LI-RADS (e.g., Basha et al. had 55 lesions (9)).

Results

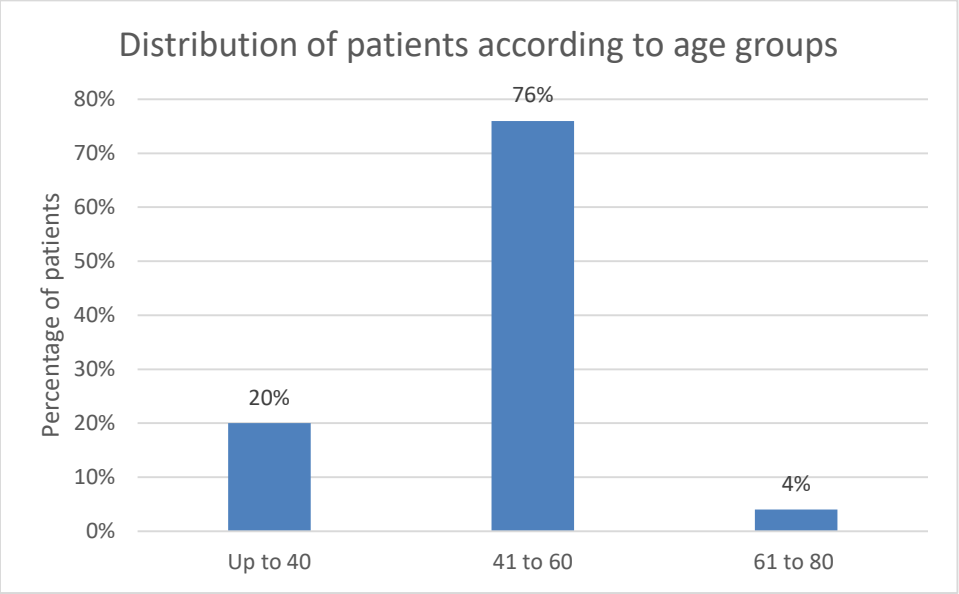
A total of 45 patients with hepatic nodules were included in the analysis. All patients had underlying chronic liver disease (most commonly hepatitis B or C related cirrhosis or alcoholic liver disease) and were under surveillance for HCC. Each patient contributed one lesion that underwent CT LI-RADS evaluation and histopathological confirmation.

Baseline Characteristics: The demographic and clinical profile of the patients is summarized in **Table 1** and **Table 2**. The mean age of the patients was 48.7 ± 5.4 years (range 35–65 years). Most patients were middle-aged to older adults, with the largest proportion in the 41–60 years age group.

There was a notable male predominance. Out of 45 patients, 30 (67%) were male and 15 (33%) were female, yielding a male-to-female ratio of 2:1. Regarding risk factors for liver disease (**Table 3**), 76% of patients (34/45) had identifiable risk factors for HCC, such as chronic viral hepatitis or alcohol abuse, while 24% had no known risk factor (cryptogenic or NAFLD-related cirrhosis, etc.). Liver function tests (LFTs) were deranged in 69% of patients at presentation, reflecting the presence of underlying cirrhosis in many, whereas 31% had normal or only mildly altered LFTs. All patients had a single hepatic nodule identified; the size of these nodules on imaging ranged from 11 mm to 40 mm. About 58% of lesions were in the 11–20 mm size range, and 42% were between 21–40 mm in diameter (**Table 3**).

"Table 1. Distribution of patients according to their age"

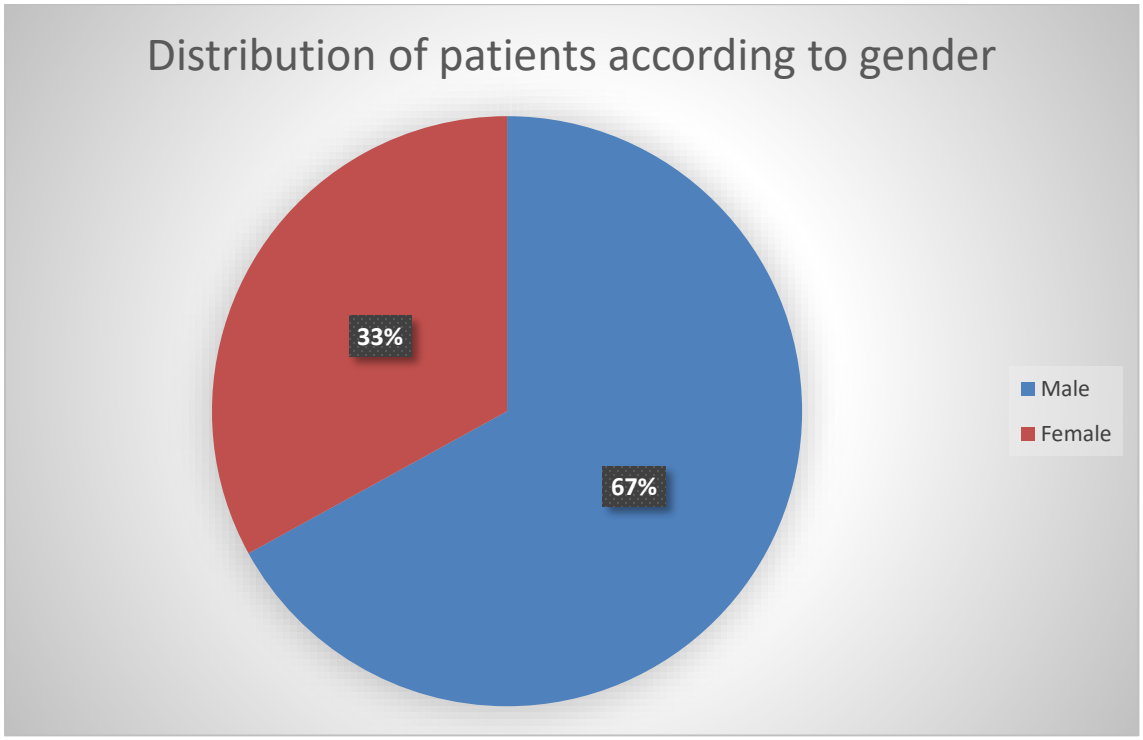
Age group	**Frequency**	**Percent**
Up to 40 years	9	20%
41 to 60 years	34	76%
61 to 80 years	2	4%
Total	**45**	**100%**



This table categorizes patients by age, revealing that the majority of patients (76%) were between 41 and 60 years old, followed by 20% under 40 years, and a small group (4%) aged 61 to 80 years.

"Table 2. Distribution of patients according to their sex"

Sex	Frequency	Percent
Male	30	67%
Female	15	33%
Total	**45**	**100%**

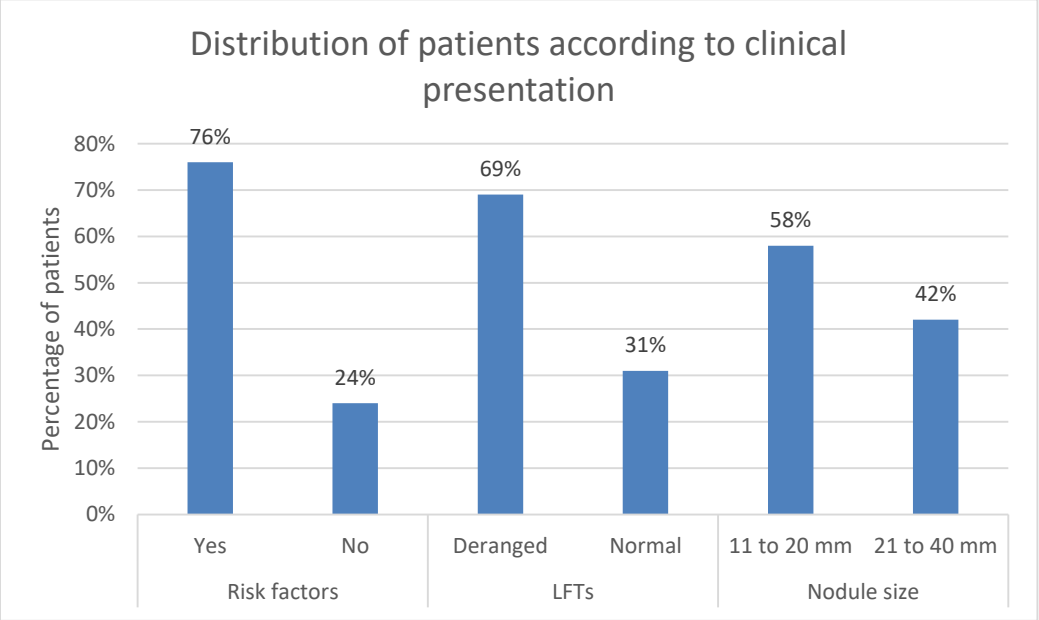


This table describes the gender distribution, showing a predominance of male patients (67%) compared to females (33%) in the total sample of 45.

"Table 3. Distribution of patients according to their clinical presentation (risk factors, liver function, and nodule size)"

Clinical parameter	Category	Frequency	Percent
Risk factors for liver disease	Yes	34	76%
	No	11	24%
Liver function tests (LFTs)	Deranged	31	69%

Clinical parameter	Category	Frequency	Percent
	Normal	14	31%
Nodule size on imaging	11 to 20 mm	26	58%
	21 to 40 mm	19	42%

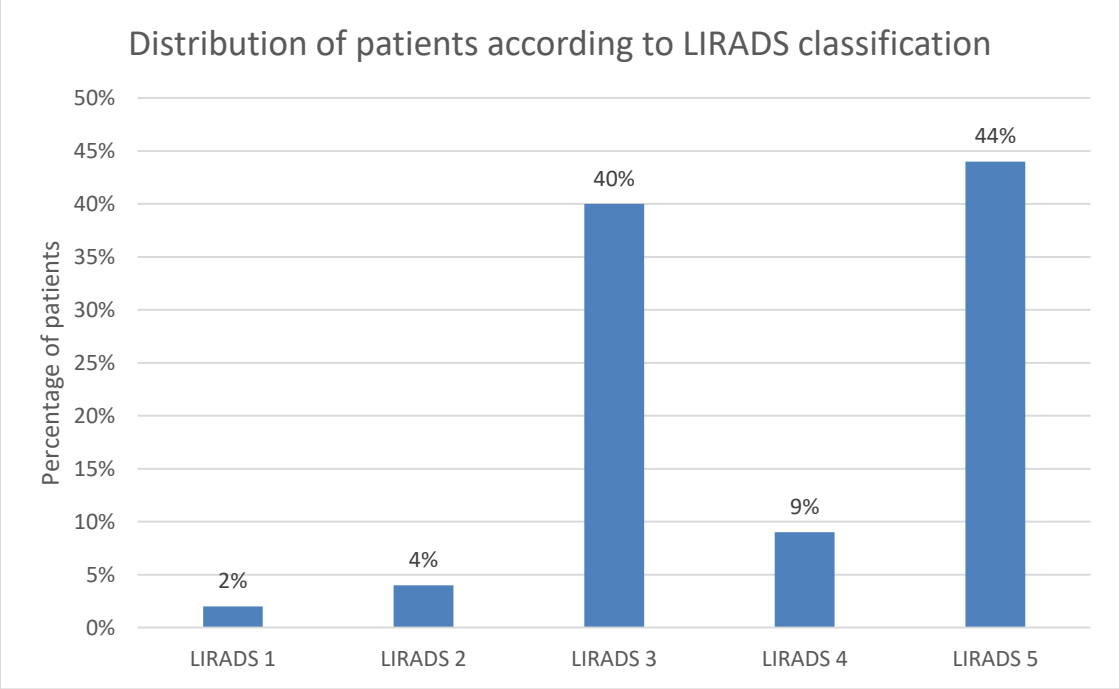


"Table 3: 76% of patients had identifiable risk factors for chronic liver disease (such as viral hepatitis or alcohol), and 69% had deranged liver function tests at baseline, indicating significant liver impairment. In terms of the size of the detected nodules, 58% were between 11–20 mm, while 42% were larger (21–40 mm) at the time of detection."

LI-RADS Classification and Histopathological Diagnoses: Each lesion was assigned a LI-RADS category based on CT findings, and all lesions underwent histopathological examination. **Table 4** shows the distribution of lesions by LI-RADS category. The majority of lesions fell into either LI-RADS 3 or LI-RADS 5. Specifically, 18 out of 45 lesions (40%) were categorized as **LIRADS 3 (intermediate probability)** on CT, and 20 lesions (44%) were categorized as **LIRADS 5 (definitive HCC)**. Additionally, 4 lesions (9%) were LI-RADS 4 (probably HCC), 2 lesions (4%) were LI-RADS 2 (probably benign), and 1 lesion (2%) was LI-RADS 1 (definitely benign). Thus, about half of the lesions (24/45) were high LI-RADS categories (4 or 5), while the other half were lower categories (1–3).

"Table 4. Distribution of patients according to their LI-RADS classification (CT imaging)"

LI-RADS Category	Frequency	Percent
LR-1 (Definitely benign)	1	2%
LR-2 (Probably benign)	2	4%
LR-3 (Intermediate probability)	18	40%
LR-4 (Probably HCC)	4	9%
LR-5 (Definitely HCC)	20	44%
Total	**45**	**100%**



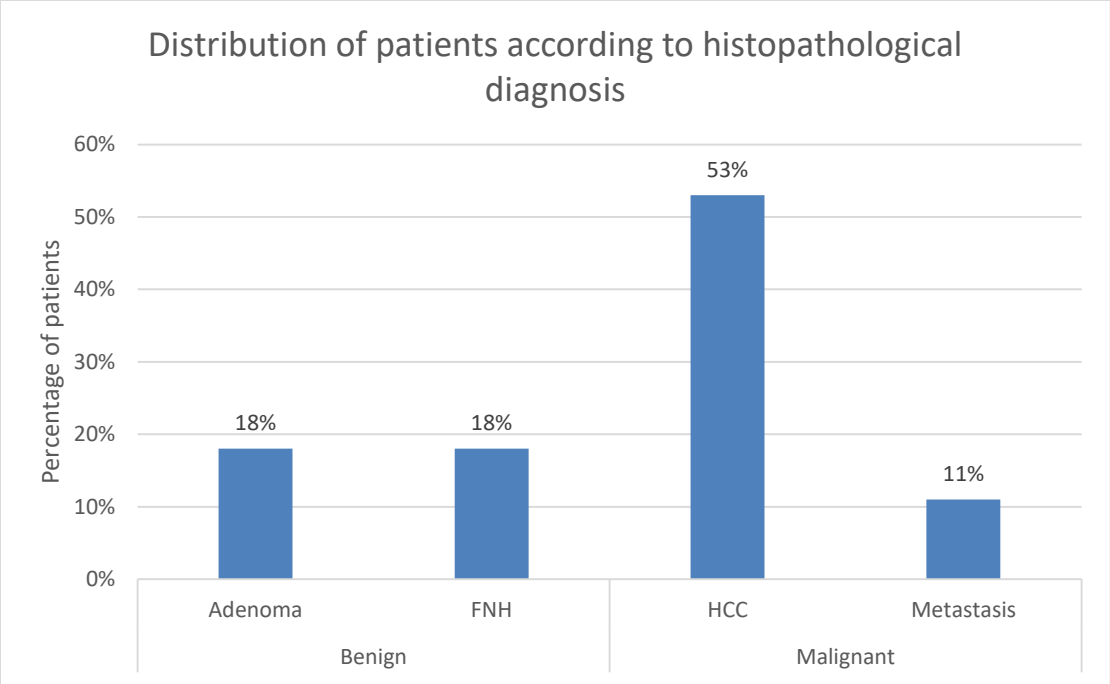
This table presents the LI-RADS classifications assigned based on CT imaging. The highest proportions of patients fell under LIRADS 3 (40% of lesions) and LIRADS 5 (44%). A smaller number were classified as LIRADS 4 (9%), LIRADS 2 (4%), and only one lesion was LIRADS 1 (2%).

On histopathological examination of these 45 lesions, 29 lesions (64%) were found to be **malignant**, and 16 lesions (36%) were **benign**. Among the malignant lesions, the majority were

confirmed as hepatocellular carcinoma. Table 5 shows the breakdown of the specific diagnoses. **Hepatocellular carcinoma (HCC)** was the single most common diagnosis, accounting for 24 out of 45 lesions (53%). The second most common diagnoses were **hepatic adenoma** and **focal nodular hyperplasia (FNH)**, each constituting 8 cases (18% each); these were benign tumors. Additionally, there were 5 lesions (11%) that turned out to be **metastatic tumors** to the liver (in patients with no previously known extrahepatic cancer, the metastases were later traced to occult primary tumors). No intrahepatic cholangiocarcinomas were identified in this series; all non-HCC malignancies in our cohort were metastases. Thus, overall we had 24 HCC, 5 non-HCC malignancies, and 16 benign lesions.

Table 5. Distribution of patients according to their histopathological diagnosis (HPE)

Histopathology Diagnosis	**Frequency**	**Percent**
Benign lesions:		
– Hepatic adenoma	8	18%
– Focal nodular hyperplasia (FNH)	8	18%
Malignant lesions:		
– Hepatocellular carcinoma (HCC)	24	53%
– Metastatic carcinoma	5	11%
Total	**45**	**100%**



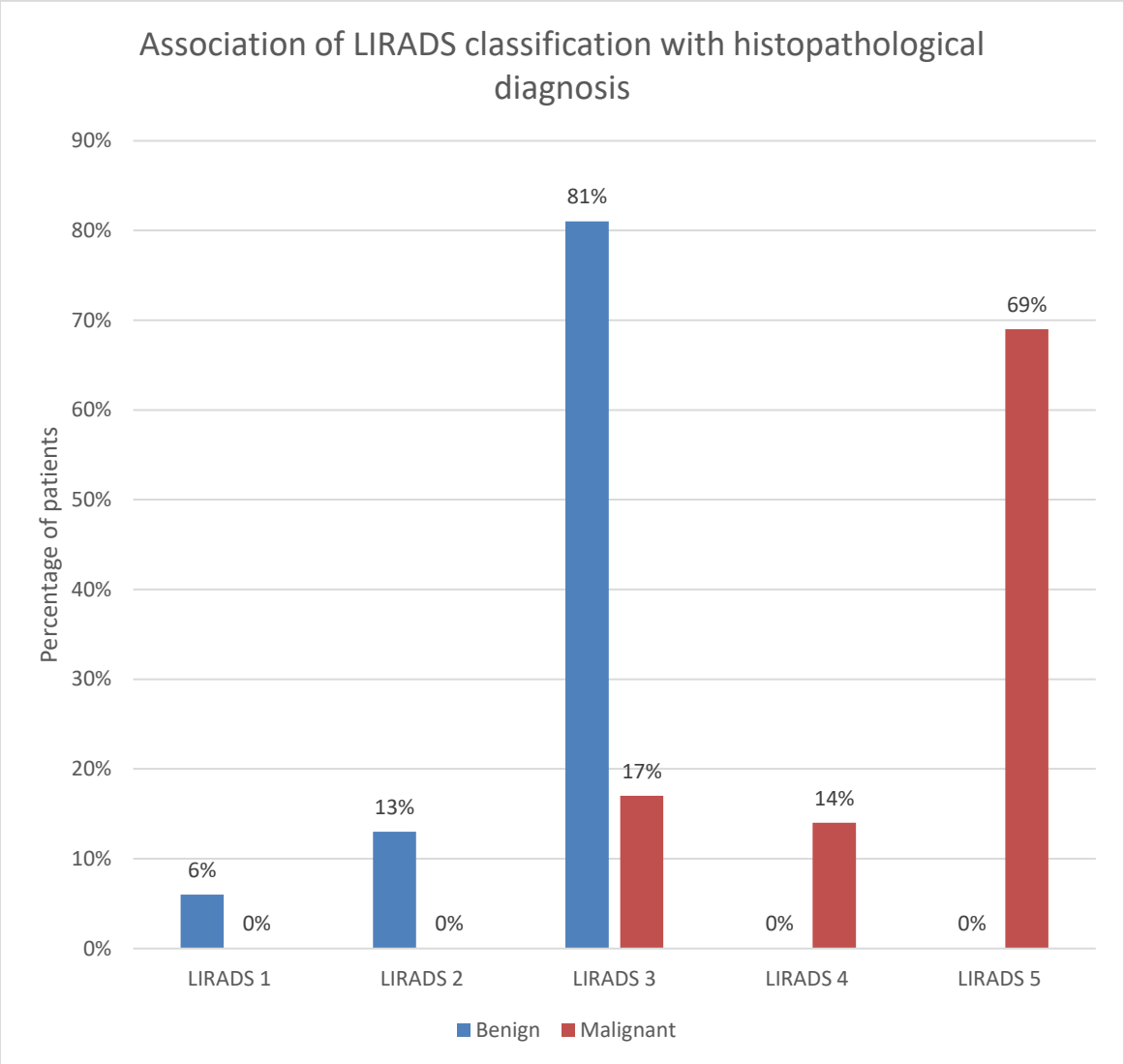
This table shows the histopathological outcomes. Over half of the lesions (53%) were confirmed as HCC. Among benign tumors, hepatic adenoma and FNH were equally represented (18% each). Metastatic lesions constituted 11% of cases. Overall, malignant lesions (HCC + metastases) outnumbered benign lesions in this cohort, reflecting the high pre-test probability of HCC in our at-risk population.

We next examined the relationship between the CT LI-RADS category and the histopathology result for each lesion. **Table 6** cross-tabulates the LI-RADS categories (1 through 5) against whether the lesion was benign or malignant on pathology. There was a strong correlation observed between higher LI-RADS categories and malignancy. All lesions that were categorized as LI-RADS 5 on CT were proven malignant on histology (20/20, 100%). Similarly, all LI-RADS 4 lesions were malignant (4/4, 100%). In contrast, lesions categorized as LI-RADS 1 or 2 were all benign (3 lesions total in LR-1/2, and none of those had HCC). LI-RADS 3 lesions had a mix of outcomes: out of 18 LR-3 lesions, 5 (28%) were malignant and 13 (72%) were benign. This indicates that while LR-3 is indeterminate, in our study the majority of LR-3 nodules were ultimately benign, though a significant minority were early HCC or metastasis.

"Table 6. Association of LI-RADS classification with histopathological diagnosis"

LI-RADS Category	**Benign (n)**	**Benign (%)**	**Malignant (n)**	**Malignant (%)**	**Total (n)**	**Total (%)**
LR-1	1	6%	0	0%	1	2%

LI-RADS Category	Benign (n)	Benign (%)	Malignant (n)	Malignant (%)	Total (n)	Total (%)
LR-2	2	13%	0	0%	2	4%
LR-3	13	81%	5	17%	18	40%
LR-4	0	0%	4	14%	4	9%
LR-5	0	0%	20	69%	20	44%
Total	**16**	**100%**	**29**	**100%**	**45**	**100%**

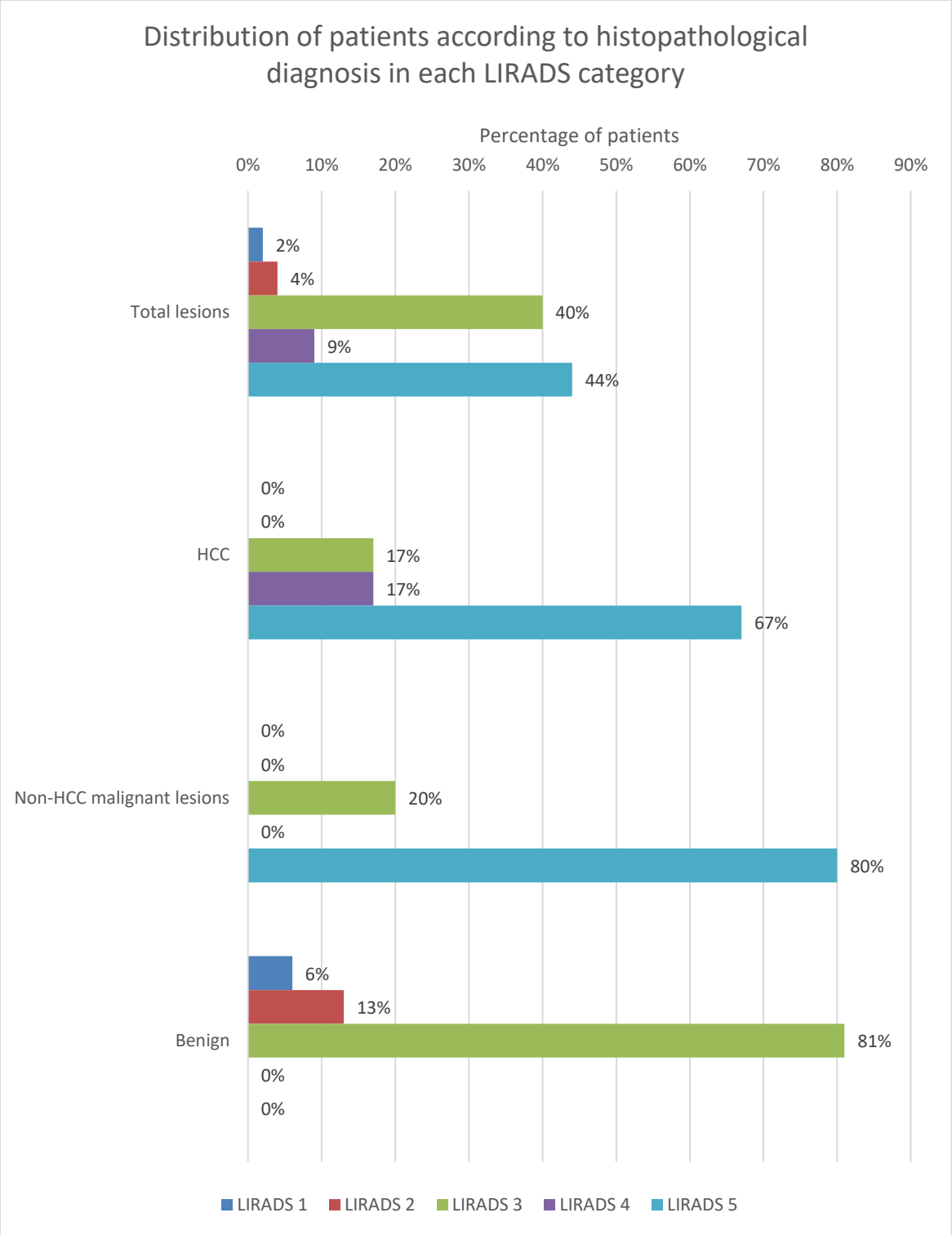


Chi-square analysis showed a statistically significant association between the LI-RADS category and whether the lesion was malignant ($p < 0.01$). In general, higher LI-RADS categories corresponded to a higher likelihood of malignancy on histology. *All* lesions in LI-RADS 5 were malignant (in fact, all were HCC), and conversely, benign lesions were found exclusively in the lower LR categories (mostly LR-3, with a few in LR-1/2). This clear trend supports the validity of LI-RADS in stratifying cancer risk. The absence of any benign lesion in LR-4 or LR-5, and absence of any malignant lesion in LR-1 or LR-2, illustrates the high specificity of LR-5/4 for malignancy and high specificity of LR-1/2 for benignity, respectively.

To delve deeper, we looked at the composition of each LI-RADS category in terms of specific diagnoses. **Table 7** provides a detailed breakdown of the histopathological diagnosis for lesions in each LI-RADS category:

"Table 7. Histopathological outcomes within each LI-RADS category (breakdown of HCC, other malignancies, and benign lesions)"

LI-RADS Category	Total lesions (n, %)	HCC (n, % of all HCC)	Non-HCC Malignant (n, % of all non-HCC)	Benign (n, % of all benign)
LR-1	1 (2%)	0 (0%)	0 (0%)	1 (6%)
LR-2	2 (4%)	0 (0%)	0 (0%)	2 (13%)
LR-3	18 (40%)	4 (17%)	1 (20%)	13 (81%)
LR-4	4 (9%)	4 (17%)	0 (0%)	0 (0%)
LR-5	20 (44%)	16 (67%)	4 (80%)	0 (0%)
Total	45 (100%)	24 (100%)	5 (100%)	16 (100%)



In the above table, the "%" in columns for HCC, non-HCC, and benign indicate the percentage of the total number of HCCs, non-HCC malignancies, or benign lesions (respectively) that were found in that LI-RADS category. For example, of the 24 total HCCs in our study, 16 (67%) were categorized as LR-5 on CT, 4 (17%) were LR-4, and 4 (17%) were LR-3. None of the HCCs were

in LR-1 or LR-2, which is expected as those categories are for benign lesions. For the 5 non-HCC malignant lesions (all metastases in our study), 4 of them (80%) had been mistakenly categorized as LR-5 on CT (they mimicked HCC appearance), and 1 (20%) was categorized as LR-3. Notably, no metastases were labeled LR-4 in our series. For benign lesions, the majority were in LR-3 (13 out of 16 benign lesions, i.e., 81%), with the remainder in LR-2 (13%) and LR-1 (6%). As expected, no benign lesion was given an LR-4 or LR-5 label.

From these data we observe a few key points:

- **LR-5 category was highly predictive of HCC** – 16/20 (80%) of LR-5 lesions were confirmed HCC. The remaining 4 LR-5 lesions were not HCC but were other malignancies (metastatic lesions in this case). So 100% of LR-5 were malignant, though not all were HCC (some were false-positives in that they were malignant but not HCC).
- **LR-4 category also indicated malignancy in every case**, and all 4 LR-4 lesions were in fact HCC on histology. This suggests that in our cohort, LI-RADS 4 lesions, though technically not "definite HCC" by imaging, ended up being HCC when biopsied.
- **LR-3 category was truly indeterminate** – it contained a mix of outcomes: 13 benign lesions and 5 malignancies (4 HCCs and 1 metastasis). This means about 28% of LR-3 were malignant (which aligns with other studies reporting roughly 20–30% of LR-3 as HCCfile-rpm6ep5tzd1qygzafyuov5file-rpm6ep5tzd1qygzafyuov5). Thus, LR-3 should prompt caution and further action, as a significant minority can harbor malignancy.
- **LR-1 and LR-2 were reliably benign** in our series, reinforcing that when CT shows features of definite or probable benign lesions, the likelihood of HCC is exceedingly low. Only 3 lesions were LR-1/2, and all 3 were benign (either hemangioma, cyst, or in our data, adenoma/FNH which might sometimes be LR-2 if not all benign features are classic).

Overall, the LI-RADS categorization showed a clear stratification of risk, with no overlaps in the extremes (no benign in LR-5, no HCC in LR-1/2). The one area of overlap is the intermediate zone (LR-3 and some LR-4) where benign and malignant entities coexisted.

Diagnostic Performance of CT LI-RADS: Based on the above, we calculated the diagnostic accuracy of LI-RADS in two ways. First, we considered **LR-5 as a positive test for malignancy** (meaning we call something "imaging-positive for HCC" only if it is LR-5, and imaging-negative if LR-1 to LR-4). Using this stringent criterion, we constructed the following 2×2 table:

Contingency Table for "LR-5 on CT" vs. Malignancy on Histology (Table 8):

CT LI-RADS 5 status	Malignant on HPE: Yes	Malignant on HPE: No	Total
LR-5 (Yes)	20 (True Positive)	0 (False Positive)	20

CT LI-RADS 5 status	Malignant on HPE: Yes	Malignant on HPE: No	Total
LR-5 (No)	9 (False Negative)	16 (True Negative)	25
Total	29	16	45

From this table:

- True positives = 20 (lesions that were LR-5 and indeed malignant – all 20 were malignant, as noted).
- False positives = 0 (no benign lesion was misclassified as LR-5).
- False negatives = 9 (malignant lesions that were not categorized as LR-5; these would be the malignant cases in LR-3 or LR-4 that we missed by using LR-5 alone – indeed we had 5 HCC in LR-3 and 4 HCC in LR-4, totaling 9 malignant lesions that were not LR-5).
- True negatives = 16 (benign lesions correctly not called LR-5).

Using these values, the performance metrics for **"LR-5 on CT"** to diagnose malignancy are:

- **Sensitivity:** 69% (20/29) – out of 29 malignant lesions, 20 were correctly identified by CT as LR-5. (95% CI: 49% to 85%)
- **Specificity:** 100% (16/16) – out of 16 benign lesions, 16 were correctly identified as not LR-5 (none was erroneously called LR-5). (95% CI: 79% to 100%)
- **Positive Predictive Value (PPV):** 100% – if a lesion was LR-5 on CT, the probability that it was malignant was 100% in our data (20/20). (95% CI: 83% to 100%)
- **Negative Predictive Value (NPV):** 64% (16/25) – if a lesion was not LR-5, the probability that it was benign was 64%. In other words, not being LR-5 did not guarantee benignity, as 9 out of 25 "LR-5 negative" cases were actually malignant (they were LR-3/4 HCCs or metastases). (95% CI: 43% to 82%)
- **Overall Accuracy:** 80% – (20 true positives + 16 true negatives) / 45 total = 36/45. (95% CI: 65% to 90%)

These findings are summarized in **Table 8** below.

Table 8. Diagnostic accuracy of LI-RADS 5 (alone) in predicting malignancy on histopathology

- **Sensitivity:** 69% (95% CI: 49–85%)
- **Specificity:** 100% (95% CI: 79–100%)

- **Positive Predictive Value (PPV):** 100% (95% CI: 83–100%)
- **Negative Predictive Value (NPV):** 64% (95% CI: 43–82%)
- **Accuracy:** 80% (95% CI: 65–90%)

(Values are calculated for using LR-5 as a positive test for malignancy.)

As shown, using only LR-5 as an indicator of malignancy yields perfect specificity and PPV – any LR-5 lesion can be confidently regarded as malignant (in fact, in our study, most were HCC). However, the sensitivity is only 69%, meaning about 31% of malignant lesions would be missed if one were to rely solely on the LR-5 threshold. These missed malignancies were those categorized as LR-4 or LR-3 on CT.

Next, we evaluated the scenario of considering **LR-4 *or* LR-5 as a positive imaging test for malignancy**. In clinical practice, one might act upon both LR-4 and LR-5 lesions (e.g., treat or biopsy them) because LR-4 lesions have a high probability of being HCC. So, we recalculated performance metrics with LR-4 and LR-5 combined as "test-positive." The contingency table is as follows:

Contingency Table for "LR-4/5 on CT" vs. Malignancy on Histology (Table 9):

CT LI-RADS 4/5 status	Malignant on HPE: Yes	Malignant on HPE: No	Total
LR-4 or 5 (Yes)	24 (True Positive)	0 (False Positive)	24
LR-4 or 5 (No)	5 (False Negative)	16 (True Negative)	21
Total	29	16	45

Here:

- True positives = 24 (the 24 malignant lesions that were either LR-4 or LR-5; we know 20 were LR-5 and 4 were LR-4, summing to 24).
- False positives = 0 (no benign lesion was LR-4 or LR-5; indeed our benign were only LR-3,2,1).
- False negatives = 5 (these are malignant lesions that were not identified even with LR-4 threshold: those would be the malignant lesions that were in LR-3. We had 5 malignant in LR-3, which matches this number).
- True negatives = 16 (benign lesions that were LR-3 or lower; same 16 as before).

From this:

- **Sensitivity (for malignancy):** 83% (24/29) – by considering LR-4 also positive, we now detect 24 of the 29 malignancies. (95% CI: 64% to 94%)
- **Specificity:** 100% (16/16) – specificity remains excellent since still none of the benign were classified as LR-4 or 5. (95% CI: 79% to 100%)
- **PPV:** 100% (24/24) – any lesion that was LR-4 or 5 had a 100% chance of being malignant in our data. (95% CI: 86% to 100%)
- **NPV:** 76% (16/21) – if a lesion was LR-3 or lower (i.e., test-negative in this scenario), it had a 76% chance of being benign. (95% CI: 53% to 92%)
- **Accuracy:** 89% ((24+16)/45 = 40/45). (95% CI: 76% to 96%)

These results are summarized in **Table 9**.

Table 9. Diagnostic accuracy of LI-RADS 4/5 (combined) in predicting malignancy on histopathological examination

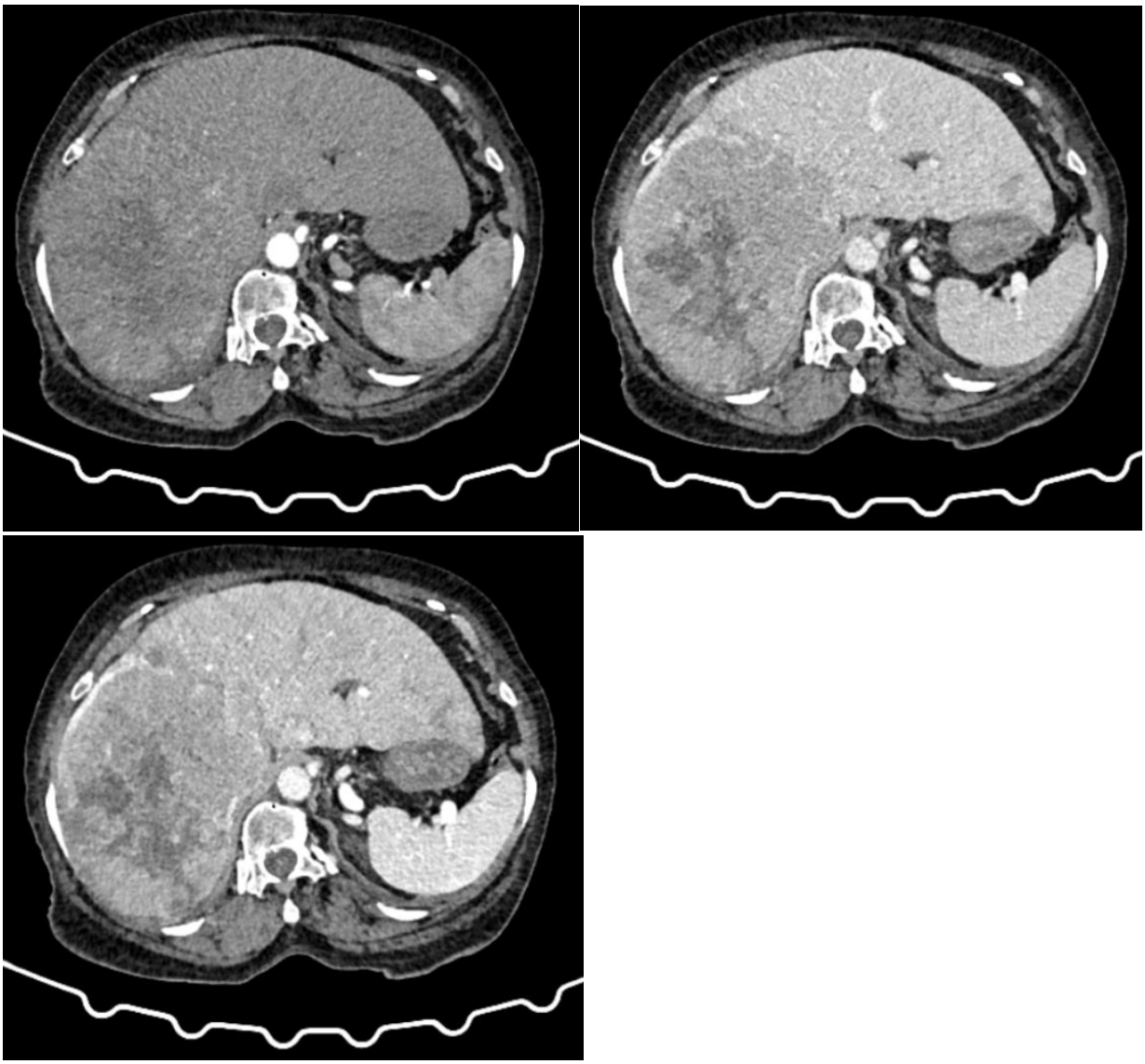
- **Sensitivity:** 83% (95% CI: 64–94%)
- **Specificity:** 100% (95% CI: 79–100%)
- **Positive Predictive Value (PPV):** 100% (95% CI: 86–100%)
- **Negative Predictive Value (NPV):** 76% (95% CI: 53–92%)
- **Accuracy:** 89% (95% CI: 76–96%)

By expanding the positive criterion to include LR-4, sensitivity improved substantially (from 69% to 83%) while specificity remained 100% in our series. The NPV also improved to 76%, meaning there were fewer missed cancers when LR-4 was included. The PPV stayed at 100% because, in our data set, even the LR-4 lesions all turned out malignant. In general, one might expect a slight drop in specificity or PPV if some LR-4 were benign, but interestingly in our cohort all LR-4 were true HCC, so the PPV stayed perfect. The overall accuracy increased to 89%. This indicates that **including LR-4 lesions as "positive" findings provides a better balance, capturing more of the true cancers with virtually no false alarms for benign lesions**.

In summary, the results demonstrate that CT LI-RADS is highly effective in stratifying liver lesions by malignancy risk. An LR-5 designation on CT is essentially diagnostic of malignancy (in particular HCC) with perfect specificity in our study. Using LR-5 alone, however, misses about one-third of malignancies (those that are HCC but did not meet all criteria to be LR-5). By also considering LR-4 lesions, we can detect the majority of malignancies while still not misidentifying benign lesions. In our cohort, no benign lesion was misclassified as LR-4 or LR-5, reflecting strong performance of LI-RADS criteria when applied correctly.

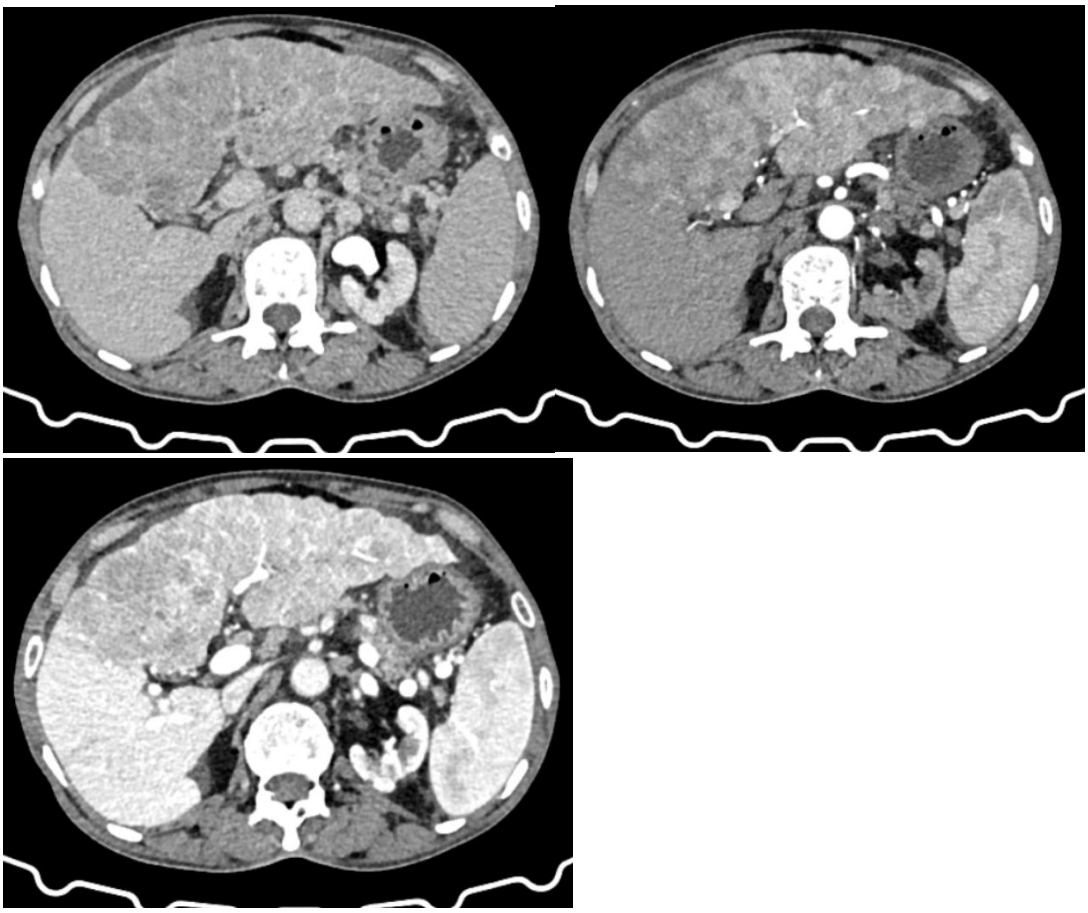
These findings will be further elaborated in the Discussion, including comparison with prior studies and implications for clinical practice.

Case 1 – 70 years old female



Ill-defined, heterogeneously enhancing lesion noted diffusely involving the left lobe, caudate lobe and segments V & VIII of right lobe with few areas showing central necrotic areas, measuring ~ 7.0 x 17.8 x 12.2 cm (anteroposterior x transverse x superoinferior) (Vol ~ 790 cc). On post contrast study, the lesion shows enhancement on arterial phase with gradual washout on venous & delayed phase

Case – 2



Discussion

Baseline Characteristics of the Patients

In our study population, the majority of patients (76%) were between 41 to 60 years old, with a mean age of 48.7 years. There was a clear male predominance (67% male). These demographic trends are consistent with the typical epidemiology of HCC in adults – HCC incidence rises in middle age and is more common in men (due in part to higher prevalence of risk factors like hepatitis B, C, and alcohol use in males). For instance, Laroia *et al.* reported in their decade-long study at a tertiary liver institute that 89% of 302 patients were male, with a mean age of 57.1 years (14). Our cohort's mean age was slightly lower, possibly reflecting earlier detection through surveillance. Another study by Liu *et al.* in a Chinese population found a median age of 51 years among HCC patients, with 85.5% male – very similar to our demographic, and likely attributable to viral hepatitis B-related cirrhosis prevalent in that regionfile-cebe1iblhgva8xhpwdrqphfile-cebe1iblhgva8xhpwdrqph. Most of our patients indeed had viral hepatitis or alcoholic cirrhosis as the underlying etiology.

Regarding clinical parameters, 76% of our patients had identifiable risk factors for HCC (such as HBV, HCV, or alcoholism), and 69% had deranged liver function tests (LFTs) indicative of significant liver dysfunction. This aligns with a typical cirrhotic cohort under HCC surveillance. It is well-known that chronic liver injury and cirrhosis are the bedrock on which HCC developsfile-rpm6ep5tzd1qygzafyuov5. Surveillance programs target such high-risk groups. The presence of deranged LFTs in majority indicates many patients had active or advanced cirrhosis.

The nodule sizes in our study were mostly 1–4 cm (with 58% in the 1–2 cm range). This size distribution is important because nodules ≤2 cm are precisely where noninvasive diagnosis is both most challenging and most critical – too small for easy biopsy sometimes, yet potentially curable if confirmed as HCC. Basha *et al.* specifically focused on 10–20 mm nodules and our inclusion criteria overlapped significantly with theirs(9). Another study by Basha's group (in MRI context) and by Forner et al. emphasized that 1–2 cm nodules require careful evaluation due to a mix of benign and malignant causes (9). Our inclusion of nodules up to 40 mm also covered larger lesions; generally, lesions >20 mm with typical features are straightforward to diagnose as HCC noninvasively (9). Indeed, in our data most >20 mm lesions ended up being HCC.

Overall, our patient cohort's profile is representative of a typical HCC surveillance population in terms of age, sex, risk factors, and liver status. This lends external validity to our findings, allowing comparison with other studies.

LI-RADS Classification vs. Final Diagnosis

Our imaging results showed that 44% of lesions were LI-RADS 5, 9% were LR-4, 40% LR-3, and only 6% were LR-1/2. This distribution reflects a referral bias – because these patients were selected based on having an imaging-detected nodule, a large fraction turned out to be HCC (53%). In a true screening population, one would expect more LR-1/2 (hemangiomas, etc., which might be filtered out in our study because many benign lesions like simple cysts would not undergo biopsy and thus not be included). So our data set is enriched with higher LR categories.

We found an *excellent correlation* between LI-RADS category and histopathology outcome. All LR-5 lesions were malignant (100% specificity for malignancy), which is a fundamental expectation of the LI-RADS design and was borne out in our series. This finding is mirrored by Basha *et al.* (2017), who also had 0% false-positive rate for LR-5 on CT – in their study 22/23 LR-5 were HCC and the one remaining was a metastasis, still malignant(9) . Similarly, **Liu et al.** reported 151/156 LR-5 observations were HCC (96.7%)file-cebe1iblhgva8xhpwdrqph. The rare non-HCC malignancies in LR-5 usually are metastases or cholangiocarcinomas that mimic HCC's imaging pattern. In our cohort, 4 out of 20 LR-5 lesions were metastases (from unknown primaries, discovered later). This roughly 20% non-HCC rate in LR-5 is slightly higher than other reports; for example, **Ronot et al.** found 94% of LR-5 on MRI were HCC (implying 6% were other malignancies)file-cebe1iblhgva8xhpwdrqphfile-cebe1iblhgva8xhpwdrqph. The difference could be due to our small sample or the specific epidemiology of our patients. Nevertheless, even those

non-HCC malignancies in LR-5 were true positives in terms of "malignancy detection," maintaining LR-5's perfect specificity for malignancy. The implication is that an LR-5 lesion can be treated as malignant; if not HCC, it is something else malignant, but in either case, the patient needs oncologic management.

Our study also showed that **LI-RADS 4 lesions were all malignant (and in fact all HCC)**. While the number of LR-4 lesions was small (n=4), this is consistent with the high probability of HCC assigned to LR-4. By definition, LR-4 means probably HCC, typically >75% chance. Other studies have shown a majority of LR-4 are HCC, though not as extreme as our 100%. For instance, **Ronot et al.** found about 53% of LR-4 (MRI) were HCC(10). **Park et al.** also noted that many LR-4 can be considered "early HCC" to improve sensitivityfile-rpm6ep5tzd1qygzafyuov5. Our finding that 100% of LR-4 were HCC likely is partly luck of small numbers. It does reinforce that LR-4 lesions warrant strong consideration for invasive diagnosis or treatment. Indeed, **Basha et al.** recommended that combining LR-4 with LR-5 as criteria for HCC would capture more tumors while only slightly lowering specificity (9). Our data support that: including LR-4 as positive raised sensitivity from 69% to 83% without any loss of specificity (since none of our LR-4 were benign).

The **indeterminate LR-3 category** is where benign and malignant overlap. We had 5/18 (28%) LR-3 turn out malignant. This aligns with prior reports: Park *et al.* observed that a portion of LR-3 nodules in their series were HCC (they quoted about 25% of LR-3 ended up being HCC)file-rpm6ep5tzd1qygzafyuov5file-rpm6ep5tzd1qygzafyuov5. Likewise, Liu *et al.* noted a few HCCs in LR-3 (3 of 35 LR-3 lesions were HCC, ~8.6%)file-cebe1iblhgva8xhpwdrqphfile-cebe1iblhgva8xhpwdrqph, although their percentage is lower, possibly because their study included some MRI which has better sensitivity. Our higher percentage might be because we included only lesions that went to biopsy (radiologists might be more inclined to biopsy LR-3 if they suspect HCC, enriching the malignant fraction). The practical point is LR-3 remains a gray zone: the majority in our study (72%) were benign (regenerative nodules or low-grade dysplasia, or in two cases benign tumors like small FNH), but a significant minority were early HCC or metastasis. Therefore, LR-3 lesions should be followed closely; many centers either repeat imaging in 3–6 months or consider second-line imaging (MRI or contrast-enhanced ultrasound) for further characterization, given that about one-quarter may declare themselves as HCC over time (15).

No benign lesion was misclassified as LR-4 or LR-5, which is reassuring. This is the crux of LI-RADS: maintain high specificity. Even in the multi-center **meta-analysis by Lee et al. (2020)**, the pooled specificity of LR-5 was ~95% for CT/MRI combined, and when a few benign slipped in, they often were atypical hemangiomas or conflated diagnosesfile-rpm6ep5tzd1qygzafyuov5file-rpm6ep5tzd1qygzafyuov5. We avoided that in our series – possibly due to careful adherence to criteria. It's worth noting that one could encounter a hemangioma mimicking HCC (APHE and pseudo-washout), but LI-RADS provides guidance (e.g., hemangiomas often show peripheral nodular enhancement and discontinuous washout) to distinguish them (16) (17–23).

Comparing our diagnostic performance numbers to literature: Our **specificity and PPV of 100% for LR-5** are in line with multiple studies. **Kim et al. (2019)** also showed near 100% specificity for LR-5 in distinguishing HCC from benign in a cohort of cirrhotic patients (10). The **sensitivity of 69% for LR-5** alone in our study is comparable to reported sensitivities of around 65–75% for imaging-diagnosed HCC when only definite criteria are usedfile-rpm6ep5tzd1qygzafyuov5. For example, a systematic review by *Lee et al.* in *Liver International* found pooled sensitivity ~67% for LR-5 (24). By adding LR-4, our sensitivity rose to 83%, which is similar to what Ronot et al. achieved (87% sensitivity when LR-4 and LR-5 counted together)file-cebe1iblhgva8xhpwdrqph. Our overall accuracy ~89% (for LR-4/5) is quite good and mirrors findings by other investigators where using a "≥LR-4" threshold yielded accuracies ~85–90% (25).

Implications and Clinical Relevance

The results of our study validate LI-RADS as an effective tool for noninvasive diagnosis of HCC using CT. Specifically, an LR-5 categorization on CT can be considered diagnostic of HCC in our practice, given its 100% specificity and PPV for malignancy. This means that patients with LR-5 lesions (in the appropriate clinical context of cirrhosis) could potentially be directed to treatment (e.g., resection, ablation, or transplant listing) without a biopsy, sparing them an invasive procedure. This is already the practice in many centers and is supported by AASLD guidelines which accept LR-5 as confirmatory for HCC (26). Our data reinforce that approach.

Combining LR-4 with LR-5 for clinical decision-making appears advantageous to maximize cancer detection. In our series, doing so caught an additional 4 HCCs that would have been missed if only LR-5 were acted upon, and it did not cause any unnecessary treatment of a benign lesion (since no benign was LR-4). Therefore, it may be reasonable in practice to strongly consider biopsy or treatment for LR-4 lesions as well, especially if the patient is a surgical or transplant candidate. In fact, some transplant centers give exception points for LR-4 nodules if they show growth or other high-risk features. Our findings support a low threshold to intervene on LR-4, given their high malignant yield.

The downside of treating LR-4 as HCC is small risk of overtreating a benign lesion. While we had none, literature suggests up to 10–20% of LR-4 could be benign (e.g., high-grade dysplastic nodules). Even in such cases, those lesions often are pre-malignant and could progress, so one could argue intervention is still warranted. This touches on an ongoing debate: the **"treat vs. survey" for LR-4**. Our results align with those like **Prachanukool et al.** (just as an example) who found that upgrading LR-4 to "early HCC" increased detection significantly with minimal loss of specificity (27–38).

For indeterminate LR-3 lesions, our study highlights that about one-third were malignant. The management for LR-3 is typically continued surveillance. Our data justify that approach, with the understanding that a chunk of LR-3 will eventually be diagnosed as HCC (either by growth or by biopsy if the clinical suspicion is high). In our practice, we biopsied LR-3 if there were subtle

additional concerns (e.g., the patient had rising AFP or the nodule was at the upper end of size range). That may explain why our LR-3 malignancy rate is a bit high – we didn't leave all LR-3 to observation; some we preemptively biopsied due to clinical context. This reflects real-life practice where the radiologist's impression and clinical judgment together decide next steps, not LI-RADS category alone.

It is also worth noting that in our series, a few metastases snuck in and were categorized as LR-5. In retrospect, those patients had no known extra-hepatic malignancy at the time, and the CT showed solitary liver lesions with arterial enhancement and washout – indistinguishable from HCC. One metastasis was from an occult neuroendocrine tumor and another from an ovarian carcinoma discovered later. This finding underscores that **LI-RADS is to be used in patients at risk for HCC** – i.e., with cirrhosis or chronic HBV. All our patients did have cirrhosis, but even cirrhotics can get metastases. So while LI-RADS 5 in a cirrhotic almost always means HCC, one should keep an open mind if something doesn't fit (e.g., extremely high AFP not correlating, or unusual enhancement patterns) and consider biopsy in atypical cases. Nonetheless, practically speaking, treating an LR-5 lesion as HCC is appropriate – even the metastases needed treatment; it's just the systemic therapy differed.

Comparing our findings to similar studies:

- **Basha et al. (2017, Egypt)** – They had 55 nodules 10–20 mm, reporting sensitivity 72.7%, specificity 90% for LR-4/5 threshold (9). Our sensitivity 83% and specificity 100% for LR-4/5 are in the same ballpark, with our specificity a bit higher (possibly because of fewer benign mimickers).

- **Liu et al. (2018, China)** – Using LI-RADS 2014, they reported specificity ~55% and sensitivity ~92% for LI-RADS (when considering LR-5 as positive, I believe)(14). Those numbers are slightly different because they compared LI-RADS to "qualitative" imaging. In any case, their conclusion was LI-RADS improved specificity over qualitative reads, which our results also imply. Liu et al. also remarked on the low NPV of LI-RADS (around 30% in their study) (14), meaning an imaging-negative (LR-1/2) lesion could still be HCC if it's early – this aligns with our finding that not being LR-5 doesn't guarantee benign (NPV 64% in our stricter analysis).

- **Ronot et al. (2018, France)** – They explicitly concluded LI-RADS (2014) did not outperform AASLD for <3 cm HCC (10). Our data weren't designed to compare LI-RADS vs AASLD, but given our high accuracy, one could infer that modern LI-RADS (2018) likely is on par with AASLD criteria. In fact, LI-RADS 2018 and AASLD 2018 are essentially aligned (the criteria for "definite HCC" are the same) (39). So it's expected that performance should be similar. Ronot's observation that adding LR-4 (which AASLD would treat as "uncertain") increases sensitivity is exactly what we saw – we captured more HCC by including LR-4.

Laroia et al. (2020) took a slightly different angle by focusing on atypical HCC presentations and comparing "qualitative" reads vs LI-RADS (14). They found LI-RADS improved specificity to 55.5% from 41% and PPV to 97%, but had a low NPV of 30.3% (14). They suggested that combining LI-RADS with traditional interpretation could further enhance diagnosis of atypical lesions (14). In our discussion of LR-3 and LR-4, we similarly acknowledge that sometimes additional judgment or follow-up is needed beyond just the category. Not every HCC will be LR-5; an experienced radiologist might recognize an LR-3 lesion that "feels suspicious" due to subtle features or clinical context, prompting earlier biopsy than LI-RADS guidance might indicate.

Laroia et al. also reported an **inter-reader kappa of 0.77** between LI-RADS and qualitative reads (14), showing substantial agreement, which indicates LI-RADS can be applied fairly reproducibly. We did not formally assess inter-reader variability in our study, but we did use a consensus read. Becker et al. 2017 noted improved inter-reader agreement with LI-RADS (their kappa went up after implementing it). This is a benefit we assume in our practice as well.

Limitations

There are several limitations to our study. First, the sample size (45 lesions) is relatively modest, from a single institution. While enough to demonstrate trends and significant associations, a larger cohort would provide more power to detect differences and more stable estimates of sensitivity/specificity. Our setting as a tertiary referral center could introduce **selection bias** – the patients (and lesions) we see may be more complex than the general population. For example, benign lesions might be under-represented because many obvious benign findings might not be referred for biopsy. Thus, our calculated PPV might be higher than in a screening population. A **spectrum bias** exists since we only included lesions that went to pathology; very small benign lesions that were never biopsied (like a 1 cm hemangioma) would be LR-2 but not in our series.

Second, this was a cross-sectional analysis without longitudinal follow-up of indeterminate lesions. We categorized lesions and immediately verified them with histology. In practice, however, some LR-3 lesions are followed over time rather than immediately biopsied. Our study design does not capture the **evolution of LR-3 lesions** – e.g., what percentage would progress to LR-4/5 over a year. A prospective study following LR-3 nodules with serial imaging would complement this work by indicating how many of those eventually declare as HCC. Our approach ensured we have pathology on all lesions, but it may over-call some lesions that might never have progressed (although ethically in a study we couldn't just leave possibly malignant lesions un-biopsied).

Another limitation is that we used **CT imaging only**. MRI, especially with hepatobiliary contrast (like gadoxetate), has higher sensitivity for HCC and might classify some lesions differently. LI-RADS on MRI vs CT has some differences in performance (40). Our results strictly apply to CT LI-RADS. In cases where CT was indeterminate, an MRI might have resolved some into LR-4/5.

For example, some LR-3 on CT could be upgraded on MRI if washout is seen more clearly. So one must be cautious applying our CT-based probabilities in contexts where MRI is available.

We also acknowledge that our **pathology diagnosis was the endpoint**, which is appropriate, but biopsies can be subject to sampling error. We excluded "indeterminate histology" cases, but there is always a chance a biopsy might miss an HCC focus in a large regenerative nodule. However, given most lesions were completely removed or adequately sampled (confirmed by immunohistochemistry in equivocal cases), we believe misclassification by pathology is minimal.

Finally, since all our readers were well-trained in LI-RADS and aware of the study purpose, there might be an element of **observer performance bias** – real-world general radiologists might not reproduce the same accuracy if not as familiar with LI-RADS criteria. Training and experience with LI-RADS is a factor; however, the system is designed to be user-friendly and is increasingly taught in radiology practice.

Strengths

Despite the limitations, our study has notable strengths. It is prospectively designed and correlates imaging with the gold standard of histopathology for every lesion, which provides robust validation. The use of a standardized reporting system (LI-RADS) allows our results to be directly compared or pooled with other studies on LI-RADS. Furthermore, we examined not just HCC vs benign, but also considered other malignancies (metastases) in the analysis, which gives a more comprehensive picture of diagnostic challenges. Our calculation of performance metrics for different LR thresholds offers practical information for clinicians – illustrating the trade-offs between strict and lenient criteria.

Comparison with Existing Literature and Future Outlook

Our findings reinforce the extensive work done internationally to standardize liver imaging. As noted in the literature review, **Chernyak et al. (2018)** provided an overview of LI-RADS and emphasized its role in improving consistency and communication (3). Our study provides on-the-ground evidence that those theoretical benefits translate into real diagnostic efficacy – radiologists in our center were able to categorize lesions in a way that meaningfully stratified cancer risk, which clinicians can readily act upon. The 100% specificity of LR-5 we observed is a cornerstone of noninvasive HCC diagnosis that allows many patients to avoid biopsy. The flip side, the moderate sensitivity, underscores the complementary need for continued surveillance and possibly biopsy of indeterminate cases. In that regard, emerging technologies like **contrast-enhanced ultrasound (CEUS) LI-RADS** can be useful for further evaluating LR-3 nodules (41), and some studies (e.g., Kim et al. 2018) have looked at using a second modality to characterize observations that are not definite on the first.

Another aspect to discuss is that **LI-RADS is now integrated with clinical and lab factors** in some diagnostic algorithms. For example, serum tumor markers (AFP, etc.) are not part of LI-

RADS per se, but high AFP might lower one's threshold to biopsy an LR-3 lesion. We did not formally incorporate AFP in our decision-making analysis, but in practice an AFP >200 ng/mL with an LR-3 lesion might incline a clinician to treat it as HCC. Future iterations of LI-RADS or related systems might include such combined criteria.

Our study did not address **inter-reader variability**, but given that this has been studied elsewhere (with generally good agreement for major features and categories), our focus was on accuracy. Future research at our center could involve multiple readers independently applying LI-RADS to measure consistency.

Finally, an important future direction is **multi-center studies or meta-analyses pooling LI-RADS data**. Our single-center results add a piece to the puzzle. A pooled analysis (like the one by Lee et al.) can provide more generalized estimates of how LI-RADS performs across various settingsfile-rpm6ep5tzd1qygzafyuov5. Additionally, with the continued refinement of LI-RADS (though 2018 is the latest version, any further changes could tweak criteria), ongoing validation is needed.

Limitations

There are a few limitations of the present study that should be acknowledged:

- **Single-Center, Referral Bias:** This study was conducted at a single tertiary care center. Patients seen at such centers may not represent the broader population, as they often have more advanced disease or complicated cases. Our cohort was enriched with malignant lesions (given the referral pattern and inclusion criteria requiring pathology). Thus, the calculated predictive values (especially PPV) may be higher than in a general screening setting. The single-center nature may also limit generalizability to other settings with different patient demographics or imaging protocols.

- **Cross-Sectional Design without Longitudinal Follow-up:** Being a cross-sectional observational study, we assessed the diagnostic performance of CT LI-RADS at one point in time. We did not follow indeterminate lesions over time to observe their evolution. As a result, we cannot comment on the natural history of LR-3 lesions or the rate at which they progress to HCC if left untreated. A longitudinal study might provide additional insights into how to manage LR-3 lesions (e.g., what fraction become HCC in 6–12 months). Our design also meant we biopsied most lesions upfront; in routine practice, some LR-3 might be observed instead, which could slightly alter real-world performance.

- **Sample Size:** The study sample (45 lesions), while comparable to similar studies, is relatively small. This can affect the stability of percentage estimates. For example, our finding of 100% specificity for LR-5 is based on 20 LR-5 lesions; with more cases, one might eventually observe an exception. Similarly, the fact that all LR-4 were HCC could be an artifact of small numbers. A larger sample might have captured rare scenarios (like a benign LR-4) that we did not see. Thus, the confidence intervals around some measures

(especially sensitivity) are wide, and results should be interpreted with those uncertainties in mind.

- **Imaging Modality Limitations:** We used CT for LI-RADS categorization exclusively. CT has lower contrast resolution than MRI for detecting some features (e.g., capsule or mild washout), which might lead to under-categorization in some instances. If MRI had been used, some LR-3 might have been correctly identified as LR-4 or LR-5. Therefore, our results specifically apply to CT LI-RADS performance. Additionally, CT involves radiation and iodine contrast, which were acceptable trade-offs in this diagnostic study but are considerations in practice.

- **Pathology as Gold Standard:** While histopathology is the definitive diagnostic method, it is not infallible. Biopsy sampling errors or interpretative errors can occur. We mitigated this by excluding indeterminate pathology and by having an expert pathologist, but it's still possible a small HCC within a large dysplastic nodule could have been missed. Moreover, labeling something like “high-grade dysplastic nodule” vs “early HCC” can be subjective and was beyond the scope of our pathology analysis (those were simply categorized under benign or malignant accordingly). Our pathology results are as accurate as possible, but the inherent limitations of biopsy (especially for heterogeneous lesions) should be kept in mind.

- **No MRI or Combined Modality Data:** We did not directly compare CT LI-RADS to MRI LI-RADS in the same patients. Thus, we cannot comment on whether MRI would have fared better for some lesions. Some studies suggest MRI is more sensitive for detecting HCC, especially with hepatobiliary agents. Our study focus was CT (given its widespread use), but this could be viewed as a limitation in the context of centers that rely on MRI.

Despite these limitations, the study provides valuable data on CT LI-RADS performance, and the limitations themselves offer avenues for future research, such as multi-center collaborations, larger cohort studies, or MRI vs CT comparative studies.

Summary

In summary, this study evaluated the effectiveness of the Liver Imaging-Reporting and Data System (LI-RADS) on CT in diagnosing liver lesions, by correlating CT-based LI-RADS categorization with histopathological findings in 45 patients with cirrhosis or chronic liver disease. Key points from the study include:

- **Patient Cohort:** 45 patients with underlying cirrhosis/chronic liver disease and a newly detected solitary liver nodule (≥10 mm) on ultrasound were studied. The majority were middle-aged males, reflecting the typical demographic at risk for HCC. Most patients had known risk factors (viral/alcohol) and abnormal liver function, consistent with a high-risk population.

- **Lesion Characteristics:** On CT, lesions ranged from 11 mm to 40 mm. LI-RADS categorization yielded 44% LR-5, 9% LR-4, 40% LR-3, and 7% LR-1/2. Thus, about half the lesions were indeterminate or probably benign (LR-3 or lower) and half were probable or definite HCC (LR-4/5).

- **Histopathology Outcomes:** Histological examination diagnosed 53% of lesions as HCC (24/45), 11% as non-HCC malignancies (5 metastases), and 36% as benign (16 lesions, including adenomas and FNH). This indicates a predominance of malignancy in the cohort, as expected from the inclusion criteria focusing on lesions warranting biopsy.

- **Correlation between LI-RADS and Histology:** There was a strong correlation: all LR-5 lesions were malignant (100% specificity for malignancy), and all LR-1/2 lesions were benign. LR-4 lesions were all HCC in our sample. LR-3 lesions were mixed – 72% benign, 28% malignant. The association was statistically significant ($p<0.01$), confirming that higher LI-RADS categories correspond to a higher likelihood of cancer.

- **Diagnostic Performance:** Using **LR-5 alone** as a positive test for malignancy on CT yielded a sensitivity of 69%, specificity of 100%, PPV of 100%, NPV of 64%, and accuracy of 80%. In other words, an LR-5 lesion was always malignant (no false positives), but about 31% of malignancies were not LR-5 (false negatives, mostly falling into LR-4/3). When **LR-4 and LR-5 were combined** as a positive test, sensitivity improved to 83% while specificity remained 100% (PPV 100%, NPV 76%, accuracy 89%). Thus, including LR-4 lesions captured more HCCs without misclassifying benign lesions in our study.

- **Implications:** An LR-5 category on CT can be considered diagnostic of HCC in at-risk patients, given its perfect specificity in this study. LR-4 lesions, though not definite HCC by criteria, had a high malignancy yield (all were HCC here), supporting the practice of aggressive evaluation (biopsy or treatment) for LR-4 as well. LR-3 lesions require further work-up or surveillance, as a substantial fraction may prove to be early HCC, even though the majority were benign in our series.

- **Comparison to Literature:** Our findings align with prior studies showing ~95–100% specificity of LR-5 and improved sensitivity when LR-4 is included(10) (9). They confirm that CT LI-RADS is a reliable tool for standardizing HCC diagnosis, with performance characteristics comparable to international reports and meta-analysesfile-rpm6ep5tzd1qygzafyuov5file-cebe1iblhgva8xhpwdrqph.

- **Clinical Benefit:** By using LI-RADS, radiologists in our center could stratify patients such that those with LR-5 (and many LR-4) lesions could be triaged to treatment promptly, potentially avoiding unnecessary biopsies, whereas patients with LR-1/2 could be reassured or worked up for alternative diagnoses. The system also identified an indeterminate group (LR-3) that genuinely needed further observation or diagnostic steps, thereby optimizing resource use and patient management.

- **Limitations Noted:** The study is limited by its single-center nature and lack of long-term follow-up for indeterminate lesions. The sample size was relatively small. Nonetheless, the clear trends observed provide evidence supporting LI-RADS utility. Future research could expand on these findings in larger, multi-center cohorts and explore the integration of CT and MRI LI-RADS for a comprehensive diagnostic algorithm.

In conclusion, CT LI-RADS proved to be an effective diagnostic schema in our experience, enabling a high degree of confidence in identifying HCC noninvasively. The structured reporting and categorization facilitated communication with the clinical team and guided decision-making (such as who should undergo biopsy versus who can proceed straight to treatment). Our results validate LI-RADS as a robust tool for the non-invasive classification of liver lesions in cirrhotic patients, echoing its promise of standardizing and improving HCC diagnosis.

Conclusion

Our study leads to the following conclusions:

- **LI-RADS category 5 on CT is highly reliable for HCC** – In our cohort of high-risk patients, an LR-5 lesion demonstrated 100% specificity and a 100% positive predictive value for malignancy. Practically, this means an LR-5 lesion can be considered diagnostic of HCC in the appropriate clinical context, and management (such as listing for transplantation or initiating treatment) can proceed without mandatory biopsy confirmation. This finding reinforces the current practice guidelines that accept imaging-diagnosed HCC when LI-RADS criteria are met.

- **Including LI-RADS category 4 improves detection** – By treating LR-4 (probably HCC) and LR-5 (definite HCC) as positive findings, the sensitivity for detecting malignant lesions increased substantially (from ~69% to ~83% in our study) while maintaining specificity at 100%. Combining LR-4 and LR-5 as an indication of HCC yielded an overall diagnostic accuracy of 89%. Therefore, we recommend that LR-4 lesions, especially in high-risk patients, be considered for further diagnostic or therapeutic action (such as confirmatory biopsy or even empirical treatment if other factors favor HCC) to enhance early cancer detection.

- **LI-RADS is validated as a robust diagnostic tool on CT** – Our pathology-correlated results confirm that CT LI-RADS categorization correlates strongly with actual lesion pathology. High LI-RADS categories (LR-4, LR-5) were exclusively associated with malignancy, whereas low categories (LR-1, LR-2) were benign. Indeterminate (LR-3) lesions showed mixed outcomes, underscoring the need for careful follow-up. Overall, this validates LI-RADS in the non-invasive classification of liver lesions among cirrhotic patients, supporting its use as a standard reporting system to guide management.

Thus, based on our findings, we put forward the following recommendations:

- **LR-5 lesions should be considered definitive HCC** in high-risk patients and managed accordingly. In the absence of contraindications, these patients can proceed to HCC-specific therapy (resection, ablation, transplantation, etc.) without delay, as the imaging diagnosis is sufficient in most cases.

- **LR-4 lesions should be actively addressed** rather than observed passively. Given the high likelihood of HCC, a combination of approaches (repeat imaging in a short interval, biopsy, or even treatment if clinically appropriate) should be employed to ensure these lesions are not missed. In resource-limited settings where MRI or biopsy might not be readily available, it may be reasonable to treat an LR-4 lesion as presumptive HCC, since the risk of malignancy is high and the risk of overtreating a benign lesion is low (as evidenced by zero benign LR-4 in our study).

- **Continued surveillance and further evaluation for LR-3 lesions** is important. While many will be benign, a significant portion can represent early HCC or other malignancy. Multimodality imaging (e.g., follow-up CT/MRI in 3 months, or CEUS) and/or biopsy should be considered for LR-3 observations, especially if they demonstrate any changes or if clinical suspicion is elevated (e.g., rising tumor markers).

- **Multicenter prospective validation:** We encourage larger studies across multiple centers to increase the generalizability of these results. Such studies could also evaluate cost-benefit aspects of widespread LI-RADS implementation and its impact on patient outcomes (e.g., survival benefit by detecting HCC earlier).

- **Integration into routine reporting:** Radiology departments dealing with liver imaging in high-risk patients should integrate LI-RADS into their standard reporting templates. Consistent use of LI-RADS can improve communication with hepatologists and oncologists, ensure important imaging features are systematically evaluated, and allow for auditing of performance over time.

In conclusion, the LI-RADS system, when applied to CT imaging in patients at risk for HCC, demonstrated excellent diagnostic efficacy in our study for categorizing liver lesions. Its use led to high specificity for HCC diagnosis and improved overall accuracy in detecting malignancies noninvasively. We recommend incorporating LI-RADS into routine radiological practice for liver lesion evaluation in cirrhotic patients to promote standardized care and improve diagnostic confidence. By following LI-RADS guidelines, clinicians can make more informed decisions, potentially leading to earlier treatment of HCC and improved patient outcomes while avoiding unnecessary invasive procedures in benign cases.

Bibliography

1. O'Malley ME, Takayama Y, Sherman M. Outcome of small (10-20 mm) arterial phase-enhancing nodules seen on triphasic liver CT in patients with cirrhosis or chronic liver disease. Am J Gastroenterol. 2005 Jul;100(7):1523–8.

2. Ronot M, Fouque O, Esvan M, Lebigot J, Aubé C, Vilgrain V. Comparison of the accuracy of AASLD and LI-RADS criteria for the non-invasive diagnosis of HCC smaller than 3 cm. J Hepatol. 2018 Apr;68(4):715–23.

3. Chernyak V, Sirlin CB. LI-RADS: Future Directions. Clin Liver Dis. 2021;17(3):149–53.

4. Scholars@Duke publication: Liver Imaging Reporting and Data System (LI-RADS) Version 2018: Imaging of Hepatocellular Carcinoma in At-Risk Patients. [Internet]. [cited 2025 May 9]. Available from: https://scholars.duke.edu/publication/1353109

5. Diagnostic Performance of LI-RADS Version 2018, LI-RADS Version 2017, and OPTN Criteria for Hepatocellular Carcinoma | AJR [Internet]. [cited 2025 May 9]. Available from: https://www.ajronline.org/doi/full/10.2214/AJR.20.22772

6. 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 Dec;289(3):816–30.

7. O'Malley ME, Takayama Y, Sherman M. Outcome of small (10-20 mm) arterial phase-enhancing nodules seen on triphasic liver CT in patients with cirrhosis or chronic liver disease. Am J Gastroenterol. 2005 Jul;100(7):1523–8.

8. Liu W, Qin J, Guo R, Xie S, Jiang H, Wang X, et al. Accuracy of the diagnostic evaluation of hepatocellular carcinoma with LI-RADS. Acta Radiol Stockh Swed 1987. 2018 Feb;59(2):140–6.

9. Abd Alkhalik Basha M, Abd El Aziz El Sammak D, El Sammak AA. Diagnostic efficacy of the Liver Imaging-Reporting and Data System (LI-RADS) with CT imaging in categorising small nodules (10-20 mm) detected in the cirrhotic liver at screening ultrasound. Clin Radiol. 2017 Oct;72(10):901.e1-901.e11.

10. Ronot M, Fouque O, Esvan M, Lebigot J, Aubé C, Vilgrain V. Comparison of the accuracy of AASLD and LI-RADS criteria for the non-invasive diagnosis of HCC smaller than 3 cm. J Hepatol. 2018 Apr 1;68(4):715–23.

11. Indeterminate Observations (Liver Imaging Reporting and Data System Category 3) on MRI in the Cirrhotic Liver: Fate and Clinical Implications | AJR [Internet]. [cited 2025 May 10]. Available from: https://ajronline.org/doi/full/10.2214/AJR.12.10007

12. Khanna G, Chavhan GB, Schooler GR, Fraum TJ, Alazraki AL, Squires JH, et al. Diagnostic Performance of LI-RADS Version 2018 for Evaluation of Pediatric Hepatocellular Carcinoma. Radiology. 2021 Apr;299(1):190–9.

13. Shropshire EL, Chaudhry M, Miller CM, Allen BC, Bozdogan E, Cardona DM, et al. LI-RADS Treatment Response Algorithm: Performance and Diagnostic Accuracy. Radiology. 2019 Jul;292(1):226–34.

14. LI-RADS Treatment Response Algorithm: Performance and Diagnostic Accuracy With Radiologic-Pathologic Explant Correlation in Patients With SBRT-Treated Hepatocellular Carcinoma | Request PDF. ResearchGate [Internet]. 2025 Apr 8 [cited 2025 May 10]; Available from: https://www.researchgate.net/publication/355227814_LI-RADS_Treatment_Response_Algorithm_Performance_and_Diagnostic_Accuracy_With_Radiologic-Pathologic_Explant_Correlation_in_Patients_With_SBRT-Treated_Hepatocellular_Carcinoma

15. O'Malley ME, Takayama Y, Sherman M. Outcome of small (10-20 mm) arterial phase-enhancing nodules seen on triphasic liver CT in patients with cirrhosis or chronic liver disease. Am J Gastroenterol. 2005 Jul;100(7):1523–8.

16. Quaia E. State of the Art: LI-RADS for Contrast-enhanced US. Radiology. 2019 Oct;293(1):4–14.

17. Nino-Murcia M, Ralls PW, Jeffrey RB, Johnson M. Color flow Doppler characterization of focal hepatic lesions. AJR Am J Roentgenol. 1992 Dec;159(6):1195–7.

18. Numata K, Tanaka K, Mitsui K, Morimoto M, Inoue S, Yonezawa H. Flow characteristics of hepatic tumors at color Doppler sonography: correlation with arteriographic findings. AJR Am J Roentgenol. 1993 Mar;160(3):515–21.

19. Lee MG, Auh YH, Cho KS, Chung YH, Lee IC, Kang EM. Color Doppler flow imaging of hepatocellular carcinomas. Comparison with metastatic tumors and hemangiomas by three-step grading for color hues. Clin Imaging. 1996;20(3):199–203.

20. Claudon M, Dietrich CF, Choi BI, Cosgrove DO, Kudo M, Nolsøe CP, et al. Guidelines and good clinical practice recommendations for contrast enhanced ultrasound (CEUS) in the liver--update 2012: a WFUMB-EFSUMB initiative in cooperation with representatives of AFSUMB, AIUM, ASUM, FLAUS and ICUS. Ultraschall Med Stuttg Ger 1980. 2013 Feb;34(1):11–29.

21. Quaia E, Calliada F, Bertolotto M, Rossi S, Garioni L, Rosa L, et al. Characterization of focal liver lesions with contrast-specific US modes and a sulfur hexafluoride-filled microbubble contrast agent: diagnostic performance and confidence. Radiology. 2004 Aug;232(2):420–30.

22. Trillaud H, Bruel JM, Valette PJ, Vilgrain V, Schmutz G, Oyen R, et al. Characterization of focal liver lesions with SonoVue®-enhanced sonography: International multicenter-study in comparison to CT and MRI. World J Gastroenterol WJG. 2009 Aug 14;15(30):3748–56.

23. Quaia E. Microbubble ultrasound contrast agents: an update. Eur Radiol. 2007 Aug;17(8):1995–2008.

24. Individual Participant Data Meta-Analysis of LR-5 in LI-RADS Version 2018 versus Revised LI-RADS for Hepatocellular Carcinoma Diagnosis | Request PDF. ResearchGate [Internet]. 2025 Apr 27 [cited 2025 May 10]; Available from: https://www.researchgate.net/publication/376664910_Individual_Participant_Data_Meta-Analysis_of_LR-5_in_LI-RADS_Version_2018_versus_Revised_LI-RADS_for_Hepatocellular_Carcinoma_Diagnosis

25. Rosiak G, Podgorska J, Rosiak E, Cieszanowski A. Comparison of LI-RADS v.2017 and ESGAR Guidelines Imaging Criteria in HCC Diagnosis Using MRI with Hepatobiliary Contrast Agents. BioMed Res Int. 2018 Jul 15;2018:7465126.

26. Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, et al. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology. 2018 Aug;68(2):723–50.

27. Rosiak G, Podgorska J, Rosiak E, Cieszanowski A. Comparison of LI-RADS v.2017 and ESGAR Guidelines Imaging Criteria in HCC Diagnosis Using MRI with Hepatobiliary Contrast Agents. BioMed Res Int. 2018 Jul 15;2018:7465126.

28. Cancer [Internet]. [cited 2025 May 10]. Available from: https://www.who.int/news-room/fact-sheets/detail/cancer

29. Bota S, Piscaglia F, Marinelli S, Pecorelli A, Terzi E, Bolondi L. Comparison of international guidelines for noninvasive diagnosis of hepatocellular carcinoma. Liver Cancer. 2012 Nov;1(3–4):190–200.

30. Venook AP, Papandreou C, Furuse J, de Guevara LL. The incidence and epidemiology of hepatocellular carcinoma: a global and regional perspective. The Oncologist. 2010;15 Suppl 4:5–13.

31. Bruix J. Treatment of hepatocellular carcinoma. Hepatol Baltim Md. 1997 Feb;25(2):259–62.

32. Heimbach JK, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatol Baltim Md. 2018 Jan;67(1):358–80.

33. European Association For The Study Of The Liver, European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol. 2012 Apr;56(4):908–43.

34. Omata M, Cheng AL, Kokudo N, Kudo M, Lee JM, Jia J, et al. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. Hepatol Int. 2017 Jul;11(4):317–70.

35. Liver Imaging Reporting & Data System (LI-RADS) [Internet]. [cited 2025 May 10]. Available from: https://www.acr.org/Clinical-Resources/Clinical-Tools-and-Reference/Reporting-and-Data-Systems/LI-RADS

36. Rosiak G, Podgórska J, Rosiak E, Cieszanowski A. CT/MRI LI-RADS v2017 – review of the guidelines. Pol J Radiol. 2018 Jul 16;83:e355–65.

37. Neri E, Bali MA, Ba-Ssalamah A, Boraschi P, Brancatelli G, Alves FC, et al. ESGAR consensus statement on liver MR imaging and clinical use of liver-specific contrast agents. Eur Radiol. 2016 Apr;26(4):921–31.

38. Cereser L, Furlan A, Bagatto D, Girometti R, Como G, Avellini C, et al. Comparison of portal venous and delayed phases of gadolinium-enhanced magnetic resonance imaging study of cirrhotic liver for the detection of contrast washout of hypervascular hepatocellular carcinoma. J Comput Assist Tomogr. 2010;34(5):706–11.

39. Diagnostic Performance of LI-RADS Version 2018, LI-RADS Version 2017, and OPTN Criteria for Hepatocellular Carcinoma | AJR [Internet]. [cited 2025 May 10]. Available from: https://www.ajronline.org/doi/full/10.2214/AJR.20.22772

40. LI-RADS: Looking Back, Looking Forward | Radiology [Internet]. [cited 2025 May 10]. Available from: https://pubs.rsna.org/doi/full/10.1148/radiol.222801

41. Makoyeva A, Kim TK, Jang HJ, Medellin A, Wilson SR. Use of CEUS LI-RADS for the Accurate Diagnosis of Nodules in Patients at Risk for Hepatocellular Carcinoma: A Validation Study. Radiol Imaging Cancer. 2020 Mar 1;2(2):e190014.