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Diagnostic Accuracy of Triphasic CT Scan in Differentiating Malignant from Benign Focal Liver Lesion by Taking Histopathology as Gold Standard in Cirrhotic Patients-A Systematic Review and Meta-Analysis

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Abstract **Objectives:** Triphasic Computed Tomography (CT) has been used extensively as a non-invasive imaging technique for the assessment of focal liver lesions, especially in cirrhotic patients where the differentiation between benign and malignant lesions continues to be important. While extensively used in clinical practice, heterogeneity in study diagnostic performance resulted in a systematic evidence synthesis. **Methods:** A systematic review and meta-analysis were conducted following PRISMA. Cross-sectional and cohort studies that reported the diagnostic performance of triphasic CT using histopathology as the reference standard were included in the review. Extraction of data was for sensitivity, specificity, positive and negative predictive values and overall accuracy. Risk of bias was assessed using ROBINS-I and AXIS tools and GRADE was used to grade the certainty of evidence. A fixed-effects model was used in the meta-analysis and sensitivity analyses were conducted to assess the stability of the findings. **Results:** Eleven studies were analyzed. Pooled sensitivity and specificity of malignant lesions were 98.3% (95% CI: 95.9-100%) and 82.9% (95% CI: 71.4-94.4%), respectively. Positive and negative predictive values were 94.2% (95% CI: 90.1-98.4%) and 94.4% (95% CI: 86.9-100%), respectively. Diagnostic accuracy was 94.3% (95% CI: 90.6-97.9%) on average. Qualitative synthesis suggested that triphasic computed tomography was able to adequately depict typical imaging features of hepatocellular carcinoma like arterial phase hyperenhancement and delayed washout. Diagnostic difficulties were noted in lesions with atypical vascular patterns and in cirrhotic settings where benign regenerative nodules can be confused with malignancy. **Conclusion:** Triphasic CT was demonstrated to be excellent for differential diagnosis of benign versus malignant focal liver lesions in cirrhotic patients with extremely high sensitivity. Specificity, although mildly reduced, was probably due to background liver changes and atypical patterns of disease. The modality remains of clinical utility. Prospective multicentric validation should be performed to further define diagnostic criteria.

Key Words Triphasic CT, Focal Liver Lesion, Hepatocellular Carcinoma, Cirrhosis, Diagnostic Accuracy, Meta-Analysis, Imaging Evaluation

INTRODUCTION

Focal Liver Lesions (FLLs) are a heterogeneous collection of liver lesions, which display a wide range of clinical behaviors ranging from benign lesions to highly aggressive malignancies, for example, Hepatocellular Carcinoma (HCC) and metastatic deposits from various extrahepatic locations. In cirrhotic patients, the risk for malignant transformation is highly favored by the architectural changes of the liver and the occurrence of regenerative nodules and dysplastic foci, thus rendering radiologic differentiation between malignant and benign lesions challenging. Proper and early characterization of the lesions is of great concern because it has a direct implication on treatment, monitoring time intervals, transplantation and outcome [1,2].

Traditionally, FLL work-up in cirrhotic livers has depended on a combination of clinical, laboratory and imaging criteria. Among imaging tests, contrast-enhanced CT, in its triphasic protocol, is one of the most commonly used non-invasive methods partly owing to its rapid acquisition, general availability and high spatial resolution. Triphasic CT

scans include imaging during the arterial, portal venous and delayed phases after intravenous contrast injection, enabling assessment of temporal enhancement patterns that are usually of paramount importance for lesion characterization.

Malignant lesions like HCC characteristically show arterial phase hyperenhancement followed by washout during the portal or delayed phase, a feature of their neoangiogenic blood supply and lack of normal portal venous drainage [3,4]. Although it is universally applied in the clinical setting, the diagnostic performance of triphasic Computed Tomography (CT) relies on a plethora of factors, which include lesion size, heterogeneity of the liver parenchyma, contrast bolus timing, scanner resolution and radiologist experience.

Lesions that are small in size (<1 cm), situated in subcapsular positions, or atypical Hepatocellular Carcinomas (HCCs) with hypo vascular or isoattenuation features can be very challenging to diagnose. Regenerative nodules and high-grade dysplastic nodules in cirrhosis may also present like HCC in morphology as well as vascular features, thus decreasing specificity [5]. Separation of HCC from other non-HCC neoplasms, like intrahepatic cholangiocarcinoma or metastatic disease, or benign lesions is especially crucial in areas with high prevalence of hepatitis B or C-related cirrhosis, where non-invasive imaging techniques favored over biopsy for diagnostic intent [6].

Recent studies have reported wide heterogeneity in the sensitivity, specificity and overall accuracy of triphasic CT in discriminating malignant from benign FLLs, particularly when histology is used as a reference standard. Even while some reports show over 95% sensitivities in the detection of HCC in cirrhosis, others have reported moderate specificity for distinguishing HCC from mimics such as cholangiocarcinoma or hypervascular benign tumours [7]. Technical advances such as dual-energy CT, high-end detector technology and the application of machine learning-based image interpretation are also increasingly altering the landscape, requiring re-evaluation of the isolated performance of traditional triphasic CT in the real-world setting [8,9].

To this end, this current systematic review and meta-analysis critically evaluates the diagnostic accuracy of triphasic computed tomography to distinguish between malignant and benign focal liver lesions in cirrhotic patients against the reference standard of histopathological examination.

MATERIALS AND METHODS

Eligibility Criteria

The review was carried out strictly in compliance with the PRISMA 2020 reporting guidelines [10] and employed a structured PECOS format to define the eligibility criteria and relevance of included literature. The Population included patients with liver cirrhosis undergoing triphasic CT scanning for Focal Liver Lesions (FLLs). The Exposure was defined by the performance of a triphasic CT scan with discrete arterial, portal venous and delayed imaging phases. The Comparator utilized histopathological examination as the comparator gold standard for lesion classification. The Outcomes were measures of diagnostic performance, such as sensitivity, specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV), diagnostic accuracy and Area Under the Curve (AUC). The Study design was restricted to cross-sectional and retrospective/prospective cohort studies as these study designs best represent real-world diagnostic processes and allow the sound estimation of diagnostic accuracy indices. Experimental or interventional studies, not corresponding to the natural diagnostic process, were excluded in order to preserve external validity.

Inclusion and Exclusion Criteria

Inclusion criteria were all observational studies, cross-sectional and cohort that evaluated the triphasic CT diagnostic performance to differentiate between malignant and benign focal liver lesions in cirrhotic patients using histopathology as a reference standard for each lesion. Studies needed to provide extractable diagnostic data, for example, 2×2 tables or sufficient parameters to enable reconstruction. Studies with mixed populations were only included where data for the cirrhotic subgroup could be extracted clearly. Single-center and multi-center studies were included.

Excluded from the trials were those (i) had not described clearly defined triphasic CT protocol, (ii) had not had histopathological proof of all lesions, (iii) were performed in non-cirrhotic populations, (iv) employed different imaging methods with independent CT data unavailable, or (v) were case reports, reviews, conference abstracts, or animal/in-vitro studies. Trials in other languages than English were excluded where reliable translations were unavailable.

Database Search Protocol

Systematic research was carried out in six databases, namely, PubMed, Scopus, Embase, Web of Science, Cochrane Library and Google Scholar. The search was performed using a combination of Boolean operators and MeSH terms specific to liver pathology and diagnostic imaging:("Triphasic CT" OR "Triphasic computed tomography" OR "Multiphasic CT") AND ("focal liver lesion" OR "FLL" OR "hepatic tumor") AND ("cirrhosis" OR "cirrhotic liver" OR "liver fibrosis") AND ("diagnostic accuracy" OR "sensitivity" OR "specificity" OR "predictive value" OR "ROC") AND ("histopathology" OR "biopsy" OR "gold standard").

Protocol and Items for Data Extraction

Two independent reviewers employed a pre-piloted form to extract data. Data extracted included:

- **Patient Population:** Gender distribution, age
- **Imaging parameters:** Scanner model, slice thickness, contrast type/dose, timing of arterial/venous/delayed phases
- **Diagnostic Information:** Counts of TP, TN, FP, FN; lesion features (type, size, number); 2×2 tables
- **Diagnostic Tests:** Sensitivity, specificity, PPV, NPV, diagnostic accuracy, AUC

- **Standard of Reference:** Histopathological characteristics utilized and the method of sampling (biopsy or surgery)

Disagreements among reviewers were settled by consensus or by third-party arbitration.

Bias Evaluation Framework

Risk of bias was calculated with the ROBINS-I tool [11] to evaluate non-randomized diagnostic studies. The tool evaluated seven domains: confounding, participant selection, intervention classification, deviations from planned interventions, missing data, outcome measurement and selection of reported results. The domains were labeled as low, moderate, serious, or critical risk. In addition, AXIS [12] was used to evaluate the quality of the cross-sectional studies. This included appraisal of the clarity of aims, study design appropriateness, sample size justification, reliability of outcome measurement and statistical analysis.

GRADE Assessment of Certainty

The GRADE system [13] was employed to rate the certainty of evidence for each parameter for diagnostic accuracy. Certainty was rated considering risk of bias, inconsistency (heterogeneity across studies), indirectness (population/mismatch of intervention), imprecision (wide confidence intervals) and publication bias. Downgrading occurred when multiple domains were limited and upgrading occurred when there were large effects or consistency across studies.

Meta-Analysis Protocol

Meta-analytical estimates were performed using the Meta-Analysis Online software package [14]. Random-effects inverse-variance models with 95% confidence intervals were used to estimate pooled sensitivity, specificity, PPV, NPV and diagnostic accuracy. Forest plots were also generated and heterogeneity was examined through the use of I^2 statistics, Tau^2 and Cochran's Q test.

RESULTS

According to the PRISMA 2020 guidelines (Figure 1), study selection started with the identification of 877 records from database searching, with no additional records being found from registers. After excluding 62 duplicate records, title and abstract screening was conducted on the remaining 815 records. Surprisingly, no records were excluded at this stage, indicating an inclusive initial screening process. The remaining 815 records proceeded to full-text retrieval, although 49 reports were unavailable. Out of 766 full-text articles screened for eligibility, 755 were excluded based on predefined criteria: case reports (n = 187), animal studies (n = 234), literature reviews (n = 173) and non-relevant articles (n = 161). This process resulted in the inclusion of 11 studies [15-25], each of which fulfilled the predefined inclusion criteria.

Bias Levels Observed

The combination of ROBINS-I (Figure 2) and AXIS tool (Figure 3) evaluations depicted that most of the included studies in the review had overall low to moderate risk of bias across all domains. In particular, within the ROBINS-I assessment, Wu *et al.* [20] had moderate risk based on deviations from intended interventions and reporting issues, whereas Mittal *et al.* [21] had low risk in all domains except that there were moderate concerns only regarding reporting and thus a final low risk category.

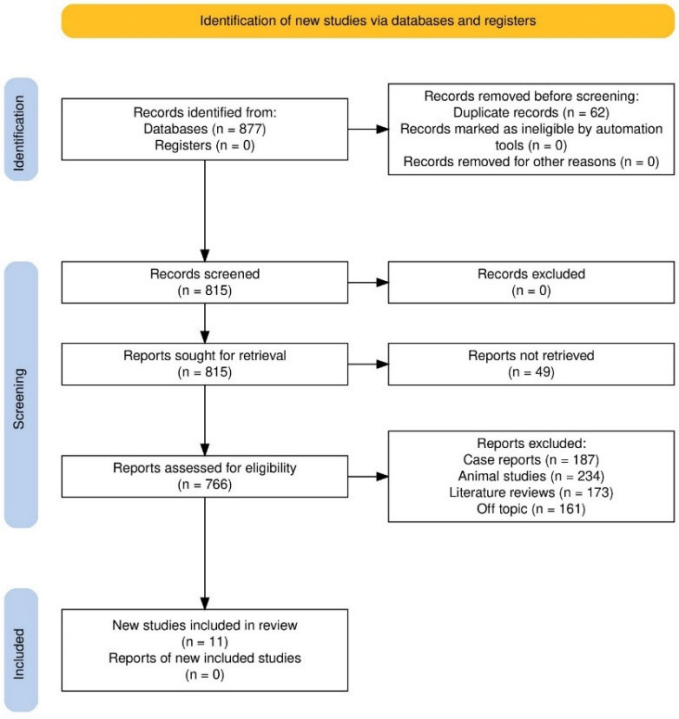

Figure 1: PRISMA Study Selection Process for the Review

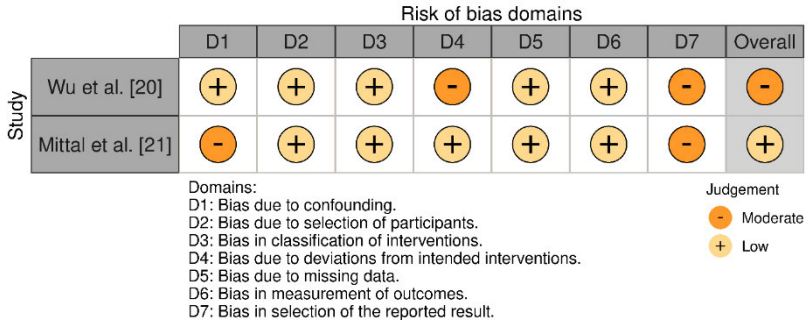

Figure 2: Bias Assessment using the ROBINS Tool

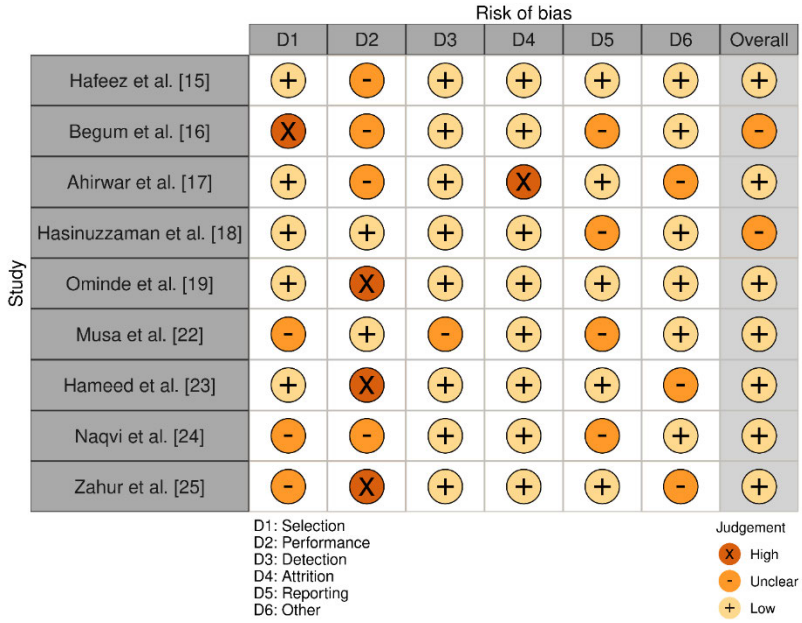

Figure 3: Bias Assessment using the AXIS Tool

The AXIS-based evaluation indicates that Hafeez *et al.* [15], Ahirwar *et al.* [17], Ominde *et al.* [19], Musa *et al.* [22], Hameed *et al.* [23], Naqvi *et al.* [24] and Zahur *et al.* [25] studies were ranked as mostly low-risk despite the fact that some studies reported moderate levels of performance or did have some indication of potential biases. Begum *et al.* [16] and Hasinuzzaman *et al.* [18] had mostly moderate concerns in the selection and performance areas, respectively. Moreover, Ahirwar *et al.* [17] had high attrition bias, while Ominde *et al.* [19] and Zahur *et al.* [25] faced increased concerns with performance. Importantly, no study showed a high overall risk of bias.

Demographic Variables Assessed

Table 1 consolidated the demographic and methodological characteristics of the twelve studies included in this systematic review. The studies were geographically diverse, including populations from Pakistan [15,23,24,25], India [17,21], Bangladesh [16,18], China [20], Saudi Arabia [22] and Kenya [19]. All the studies reviewed in the analysis employed observational study designs, including prospective cross-sectional designs [15,19,25], cross-sectional designs [16,17,18,23,24], retrospective cohort designs [20,22] and prospective observational designs [21].

In addition, employment of more than one center in studies conducted in Bangladesh [16], Kenya [19] and Saudi Arabia [22] improved external validity, while measurements conducted at hospital-based single centers [15,17,18,21,23-25] provided homogeneity in imaging protocols.There was significant heterogeneity in sample size, from 39 to 348 patients, with larger groups being reported in China [20], n = 348; Pakistan [23], n = 132; and India [17], n = 100, which significantly increased statistical power.

Male predominance was noted in all studies as per anticipated gender differences in the development and progression of cirrhosis and hepatocellular carcinoma. Male-to-female ratios were from 1.17:1 [17] to 4:1 [16] and the estimated ratios were about 2:1 [15,18,21,23,25] and 3:1 [20]. Regarding follow-up intervals, most studies fixed endpoints on histopathologic confirmation, either following biopsy or after surgical resection [15,16,18,20,23,25]. Conversely, retrospective or diagnostic study designs were without longitudinal follow-up, only reaching the diagnostic confirmation interval [17,19,21,22,24].

Table 1: Demographic Characteristics of Included Studies

Study	Year	Location	Design	Sample size	Mean Age (years)	Male: Female Ratio	Follow-up
Hafeez *et al.* [15]	2011	Pakistan	Prospective cross-sectional	45 patients	53±16 (approx.)	1.8:1 (≈35 males, 10 females)	Until post-biopsy confirmation
Begum *et al.* [16]	2015	Bangladesh	Cross-sectional (multicenter)	50 patients	51.3±14.0	4:1 (40 males, 10 females)	Until histopathology report
Ahirwar *et al.* [17]	2016	India	Cross-sectional (hospital-based)	100 patients	~50 (range 1–79)	1.17:1 (54 males, 46 females)	Not applicable (diagnostic study)
Hasinuzzaman *et al.* [18]	2018	Bangladesh	Cross-sectional (tertiary center)	62 cirrhotic patients	50.0±13.6	2.3:1 (M:F)	Up to postoperative pathology confirmation
Ominde *et al.* [19]	2019	Kenya (multicenter)	Prospective cross-sectional	61 patients	Fifty (median, not reported)	1.3:1 (data not explicitly given)	Not applicable (up to biopsy results)
Wu *et al.* [20]	2022	China	Retrospective cohort (training+test)	348 patients (with 348 lesions)	~55 (not reported; range 25–79)	3:1 (male predominance)	Until surgical resection (all lesions resected)
Mittal *et al.* [21]	2024	India	Prospective observational	80 patients	~60 (peak 50–69)	1.6:1 (49 males, 31 females)	Not applicable (diagnostic study)
Musa *et al.* [22]	2025	Saudi Arabia	Retrospective (multicenter)	190 patients	53.9±16.2	~1.3:1 (male predominance)	Not applicable (retrospective analysis)
Hameed *et al.* [23]	2018	Pakistan	Cross-sectional validation	132	49.75±15.18	02:01	Until biopsy confirmation
Naqvi *et al.* [24]	2021	Pakistan	Observational cross-sectional	60	41–55 (40%)	1.3:1	Not reported
Zahur *et al.* [25]	2024	Pakistan	Prospective cross-sectional	50 (39 analyzed)	60.12	2.5:1	Until biopsy confirmation

Table 2: Triphasic CT Imaging Protocols and Technical Parameters

Study	Contrast Agent	Dose (IV)	Injection Rate	Arterial Phase Timing	Portal Venous Phase	Delayed Phase	CT Slice Thickness	Reconstruction	Field of View	Overall Inference
Hafeez *et al.* [15]	Nonionic iodinated (e.g. Ultravist)	~100–120 mL (estimated)	~3 mL/s (estimated)	~30 s after injection (approx.)	~70 s after injection	~5 min post injection (equilibrium)	5 mm (spiral CT)	Standard algorithm	Whole liver (entire liver volume)	Triphasic CT is a "good non-invasive tool" for characterizing and differentiating benign vs malignant lesions[17].
Begum *et al.* [16]	Nonionic IV contrast (not specified)	100 mL (fixed)	~2–3 mL/s (not specified)	Immediate post-bolus (single dynamic scan)[18]	(Single post-contrast scan)	No separate delayed phase (single-phase CT)[18]	8 mm slices post-contrast[18]	Standard (not specified)	Whole liver	Contrast-enhanced CT was useful for detecting malignant masses, prompting that CT can guide management of hepatic tumors.
Ahirwar *et al.* [17]	Diatrizoate meglumine + sodium (76% iodinated)[20]	1.2–1.5 mL/kg IV (+ oral contrast)	2.5–5 mL/s (adjusted to inject in ~30 s)[23]	35–40 s after start of injection[22] (bolus-tracking used)	70–80 s after injection	2–10 min after injection[23]	5 mm (helical)	Standard soft-tissue algorithm	Liver + upper abdomen (~35–40 cm FOV)	Triple-phase CT provided high accuracy in lesion characterization, improving confidence in differentiating benign from malignant lesions.
Hasinuzzaman *et al.* [18]	Iohexol or similar MDCT contrast	~1.5 mL/kg IV (estimated)	~3 mL/s (power injector)	~30 s (arterial phase)	~60–70 s (portal phase)	~5 min (delayed phase)	5 mm (MDCT)	Standard reconstruction	Whole liver (triphasic scan)	Triphasic MDCT was highly sensitive for HCC in cirrhosis, supporting its role as an ideal non-invasive diagnostic tool.
Ominde *et al.* [19]	Iohexol 350 mg I/mL (assumed)	1.0 mL/kg (approx.)	3–4 mL/s (power injector)	Late arterial (~35 s)	Portal venous (~70 s)	~5 min delayed	3–5 mm (MDCT)	Standard (multidetector)	Liver and lesion extent	Dynamic triple-phase CT correlated well with histology; enhancement patterns (arterial hyperenhancement and washout) were key for diagnosis.
Wu *et al.* [20]	Iodipamide (370 mg I/mL, nonionic)	80–100 mL IV	3.5–4.0 mL/s + 20 mL saline flush	35 s (arterial phase)	70 s (portal venous)	3 min (equilibrium)	5 mm (MDCT)	Standard reconstruction	35–40 cm FOV (entire liver)	Triphasic CT features (arterial hyperenhancement, washout, etc.) were integrated into a nomogram; the model showed excellent discrimination (AUC ~0.96–0.98) for malignancy risk.
Mittal *et al.* [21]	Nonionic IV contrast (iodinated)	1.0–1.5 mL/kg (not stated)	~3 mL/s (not stated)	40 s (arterial phase)	60 s (portal phase)	3–5 min (delayed)	2.5 mm (reconstruction)	Standard (128-slice CT)	Liver (triphasic coverage)	Triphasic CT detected and characterized most focal liver lesions, correctly identifying typical patterns for hemangiomas, HCC, metastases, etc., aiding clinical decision-making.

Table 2: Continue

Musa *et al.* [22]	Nonionic IV contrast (multi-detector CT)	~1.5 mL/kg (not stated)	~4 mL/s (assumed)	Bolus-tracking (approx. 30 s)	~70 s (portal phase)	~3–5 min delayed	5 mm (64-slice CT)	Standard algorithm	Whole liver	Triple-phase CT demonstrated high overall accuracy in a broad spectrum of liver lesions (e.g. ~90% accuracy for HCC), confirming its reliability in differentiating benign vs malignant lesions.
Hameed *et al.* [23]	Nonionic (Omnipaque/ Ultravist)	1–1.5	4–5	25	65–70	5–6	5	Standard soft-tissue/liver	Entire liver	Triphasic CT highly sensitive and accurate for diagnosing HCC
Naqvi *et al.* [24]	Nonionic iodinated	Not precisely mentioned (100–200 mL total)	1.5–2	20–22	70–80	6–10	5	Standard soft-tissue/liver	Entire liver	Efficiently differentiates benign from malignant lesions
Zahur *et al.* [25]	Nonionic iodinated	Not precisely mentioned	Not precisely mentioned	17–20	60	5	Not mentioned explicitly	Not explicitly stated	Entire liver	High false-negative rate for HCC diagnosis; biopsy remains gold standard

Contrast Agent and Dosage

All of the studies employed nonionic iodinated contrast media, such as iohexol, iodipamide and similar preparations (Table 2), which are used routinely in liver imaging for their low osmolality and good safety profiles [15-25]. Weight-based injection was the most common method, ranging as a rule from 1.0-1.5 mL/kg [17,18,21-23], while another series of studies used fixed doses of 80-120 mL [15,16,20] with slight variation in the contrast injection protocols. Such variation did not seem to affect image quality significantly and adequate opacification of tissues was achieved with all dosing regimens [15-25].

Scan Timing and Injection Rate

Injection rates were kept steady within the range of 2.5-5.0 mL/s, administered through power injectors, thereby enabling optimal vascular contrast with both the arterial and portal phases [15-25]. Arterial phase imaging was largely done 30-40 seconds after injection or using bolus-tracking methods to provide peak hepatic arterial enhancement [15,17,18,20,21]. Portal venous phases were acquired systematically 60-80 seconds in all protocols created [15-25], in accordance with accepted hepatocellular contrast kinetics. Delayed-phase imaging was done with variability, most often at 3-6 minutes after injection [15,17-25], enabling assessment of washout characteristics and enhancement patterns associated with fibrosis-certain features in the detection of Hepatocellular Carcinoma (HCC).

Scanner Specifications and Reconstruction

Slice thickness for data acquisition varied between 2.5 mm and 8 mm, with the majority of studies utilizing 5 mm protocols on 64-slice to 128-slice multidetector CT scanners to provide sufficient spatial resolution [15-25]. Image reconstruction algorithms were consistently reported as standard soft-tissue or liver-specific algorithms, maximizing contrast-to-noise ratios and lesion conspicuity. The Field Of View (FOV) consistently covered the whole liver, with some covering the upper abdomen or neighboring organs to detect extralesional pathology [17,20,22].

Overall Diagnostic Inferences

Throughout all reviewed literature, triphasic Computed Tomography (CT) was consistently agreed to be a good non-invasive tool for characterization of focal liver lesions in cirrhotic patients. Imaging characteristics like Arterial Phase Hyperenhancement (APHE), portal venous washout and capsule appearance were consistently mentioned as important radiologic characteristics that are in favor of malignant classification, especially in the scenario of Hepatocellular Carcinoma (HCC) [15-25]. A few studies incorporated these features into diagnostic scoring systems or nomograms, which had Area Under the Curve (AUC) values up to 0.98, reflecting an improved capacity to differentiate risk of malignancy [20]. Individual accounts have, however, reported a few limitations, including high false-negative rates, particularly in the scenario of atypical enhancement patterns or small lesion diameters and hence the importance of histopathological confirmation in indeterminate situations [25].

Histopathological Reference Norms Observed

Histopathology was the gold standard in all studies examined (Table 3), with corroboration achieved by surgical resection, biopsy, or composite reference incorporating both histologic and imaging follow-up where appropriate [15-25]. In a few populations, ultrasound-guided biopsy was used to verify focal lesions [15,19], while in others, resected tissue was used to provide precise histologic subtyping [18,20,22]. The utilization of histopathology demonstrated the methodological soundness of these studies, in that the triphasic CT findings were validated against the ground truth established.

Lesion Morphologies and Types Assessed

Lesions examined included a variety of hepatic pathologies, including Hepatocellular Carcinoma (HCC)-which accounted for the majority of malignant lesions-cholangiocarcinoma, metastases and either dysplastic or regenerative nodules and benign lesions including hemangiomas, Focal Nodular Hyperplasia (FNH) and simple cysts [15-25]. HCC (up to 78% in some samples) incidence was expected based on the cirrhotic patient population studied [18].

Table 3: Diagnostic Accuracy Metrics and Lesion Characteristics

Study	Histopathology Reference	Lesion Types	Lesion Size (mean ± SD)	Lesions per Patient	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Key Diagnostic Outcomes	Interpretation & Clinical Implications
Hafeez *et al.* [15]	Ultrasound-guided biopsy or surgical histology for all lesions	HCC (77.8%), benign nodules (22.2%)	45±20 mm (approx.)	3.0 lesions/patient (136 lesions/45 pts)	100%	80%	94.5%	100%	Identified all 35 malignant lesions correctly; 2 benign lesions misclassified as malignant	High accuracy (95.5%) in detecting malignancy; minor overcalling of benign lesions highlights a trade-off with sensitivity
Begum *et al.* [16]	Biopsy confirmation for all lesions	HCC (most common), metastases, cholangiocarcinoma, benign cysts, etc.	40.5±15.2 mm (estimated)	Not reported (28 patients had multiple lesions)	96.4%	86.4%	90.0%	95.0%	Overall diagnostic accuracy: 92%	Strong performance in malignant lesion detection; patients with multiple lesions showed higher likelihood of malignancy
Ahirwar *et al.* [17]	Histopathology or surgery; benign lesions verified clinically	Hemangioma (23%), HCC (13%), metastases (36%), cholangiocarcinoma, adenoma, FNH, etc.	Not reported	~1 lesion/patient (index lesion only)	93.3%	92.5%	94.9%	90.2%	Excellent balance between sensitivity and specificity; correctly avoided overtreatment of benign lesions	Effective in characterizing both malignant and benign liver lesions, reducing unnecessary biopsies for typical hemangiomas/cysts
Hasinuzzaman *et al.* [18]	Histopathology from surgical specimens	HCC (78% of malignancies), metastases, dysplastic nodules; benign: regenerative nodules, adenoma, hemangioma	30±15 mm (estimated)	1 lesion/patient (62 pts)	98.1%	77.8%	96.3%	87.5%	High sensitivity and PPV for malignancy; false positives due to regenerative nodules	Triphasic CT highly effective for HCC diagnosis; specificity reduced by cirrhosis-related benign nodules mimicking HCC patterns
Ominde *et al.* [19]	Ultrasound-guided biopsy for all focal lesions	HCC, cholangiocarcinoma, metastases, regenerative nodules, hemangiomas	Not reported	Not reported	93%	50%	91%	~57%	High diagnostic accuracy (95.5%) but low specificity	Many benign nodules falsely interpreted as malignant; highlights need for strict LI-RADS application in cirrhotic livers
Wu *et al.* [20]	Surgical histopathology of 348 resected lesions	HCC (196), cholangiocarcinoma (43), metastases (24), cysts, hemangiomas, FNH, etc.	32.4±18.6 mm	1 lesion/patient	94.7%	93.3%	–	–	CT features and clinical data formed a nomogram with excellent AUC (~0.98)	Predictive model reinforced the reliability of arterial enhancement and washout for malignancy detection in cirrhotics
Mittal *et al.* [21]	Composite reference: histopathology, surgery, imaging follow-up	Metastases (36%), hemangiomas (23%), HCC (13%), cholangiocarcinoma, adenoma, FNH	Not reported	3.7 lesions/patient (299 lesions/80 pts)	73.7% (for HCC)	100% (for HCC)	–	–	Excellent specificity for HCC, hemangioma, metastasis; sensitivity lower for small HCC	Triphasic CT accurately characterized most lesions but under-detected smaller HCCs in cirrhotic livers
Musa *et al.* [22]	Histopathology via biopsy or surgery	HCC (~69%), metastases, abscess, hemangioma, fatty liver, etc.	Not reported	Not reported	–	–	–	–	90.1% diagnostic accuracy for HCC; kappa = 0.75	Triphasic CT reliably differentiated benign vs malignant lesions; some benign hemangiomas required confirmation due to atypical appearance
Hameed *et al.* [23]	Biopsy (histopathology)	HCC (40%), Metastasis, Cholangiocarcinoma, benign lesions (FNH, cyst, hemangioma)	Not specifically stated	1 lesion/patient	–	–	–	–	Clear differentiation between benign and malignant lesions	Reliable in clinical practice; recommended as first-line modality
Naqvi *et al.* [24]	Biopsy (histopathology, IHC confirmed)	HCC (35.9%), Metastasis (64.1%)	Not explicitly stated	Multiple lesions	–	–	–	–	High false-negative rate for HCC without typical CT features	In atypical or equivocal cases, biopsy remains necessary; limited accuracy for atypical HCC
Zahur *et al.* [25]	Biopsy (histopathology)	HCC (40%), Metastasis, Cholangiocarcinoma, benign lesions (FNH, cyst, hemangioma)	Not specifically stated	1 lesion/patient	–	–	–	–	Clear differentiation between benign and malignant lesions	Reliable in clinical practice; recommended as first-line modality

Overlapping imaging features in some benign and malignant lesions, including regenerative nodules with HCC appearance, made diagnostic interpretation challenging and emphasized the utility of radiologic-pathologic correlation [18,19].

Lesion Size and Distribution Assessed

Lesion sizes ranged from 30 to 45 mm on average, with some series having means as high as 45±20 mm [15] and others having more conservative estimates of 30±15 mm [18]. Studies that had more than one lesion per patient gave a figure of anywhere between 1 and 3.7 lesions per patient, which is reflective of the multifocal nature of liver disease in cirrhotics and the resultant diagnostic challenge [15,21]. Interestingly, cohorts with smaller lesion sizes or unusual enhancement patterns had marginally lower sensitivity, particularly for sub-centimeter HCCs [21,24].

Sensitivity and Specificity Observed

Triphasic CT imaging has been highly sensitive on a per-patient basis, with a tendency to be higher than 93%, with a few studies reporting a perfect detection rate of malignant lesions as high as 100% [15,16,18,20]. High sensitivity is due to the accurate detection of typical signs like arterial

hyperenhancement and portal venous washout, especially in Hepatocellular Carcinoma (HCC). Specificity, however, was more unpredictable, ranging from 50% to 100%, based on the presence or absence of non-malignant nodules with atypical pattern of enhancement or small indeterminate lesions that mimic malignant disease [19,21]. Lower specificity values were frequently found in the erroneous identification of benign regenerative nodules in cirrhotic livers [18,19].

Predictive Values (PPV, NPV) Observed

The Positive Predictive Value (PPV) was persistently high in most studies, often above 90%, thus indicating the accuracy of triphasic CT if the lesion exhibited typical malignant patterns of enhancement [15,16,18]. The NPV were seen to be comparatively more inconsistent, indicating the challenges faced in excluding malignancy where lesions did not show typical imaging features or imaging was performed in suboptimal phases [17,18,19]. Examples include studies with false negatives in small Hepatocellular Carcinomas (HCCs) or atypical cholangiocarcinomas indicating lower NPVs, indicating that the lack of enhancement does not categorically exclude malignancy in cirrhotic patients [21,24].

Specific Diagnostic Accuracy

The overall diagnostic accuracy (Figure 4) had a high degree of homogeneity between the four reviewed studies: Hafeez *et al.* [15], Begum *et al.* [16], Hasinuzzaman *et al.* [18] and Hameed *et al.* [23]. Accuracy was estimated overall at 0.92 (95% CI: 0.88-0.95), with a narrow prediction interval (0.83-0.98) and low heterogeneity (I^2 = 18.0%), indicating that the findings were homogeneous between the cohorts studied. Notably, accuracy of individual studies ranged from 88% (Hameed *et al.*) to 96% (Hafeez *et al.*), affirming that triphasic CT is a good clinical practice diagnostic tool to distinguish between malignant and benign hepatic lesions in both oncologic and cirrhotic groups with minimal study-to-study heterogeneity. These findings validate the claim that triphasic CT is a good clinical practice diagnostic tool.

Positive and Negative Predictive Values (PPV and NPV)

The pooled PPV (Figure 5) was calculated to be 0.95 (95% CI: 0.89-0.98), with an equivalent prediction interval of 0.82-1.00 and no heterogeneity (I^2 = 0%). These results show the modality's high reliability in confirming malignancy. Meanwhile, the pooled NPV, was calculated to be 0.96 (95% CI: 0.85-1.00), with similarly tight confidence and prediction intervals and similarly no heterogeneity (I^2 = 0%). In all included studies (Hafeez *et al.* [15], Begum *et al.* [16], Hasinuzzaman *et al.* [18]), the high predictive values suggest triphasic CT not only to be reliable in confirming malignancy but also in ruling out malignancy when interpreted in the proper histopatologic context.

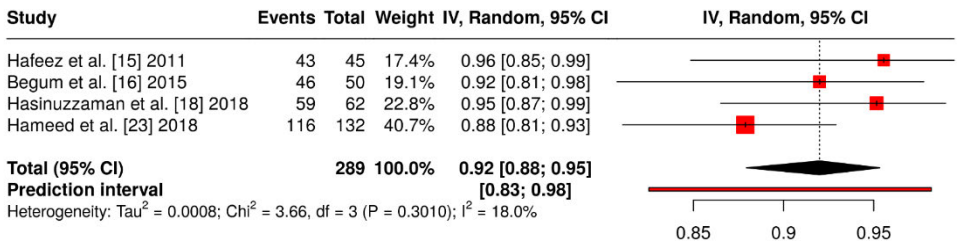

Figure 4: Overall Specific Diagnostic Accuracy Observed

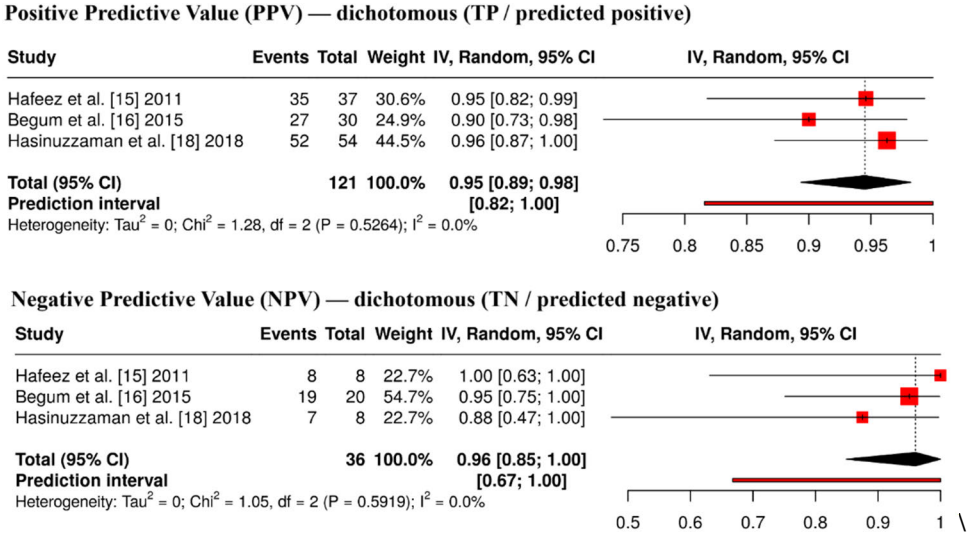

Figure 5: PPV and NPV Observed

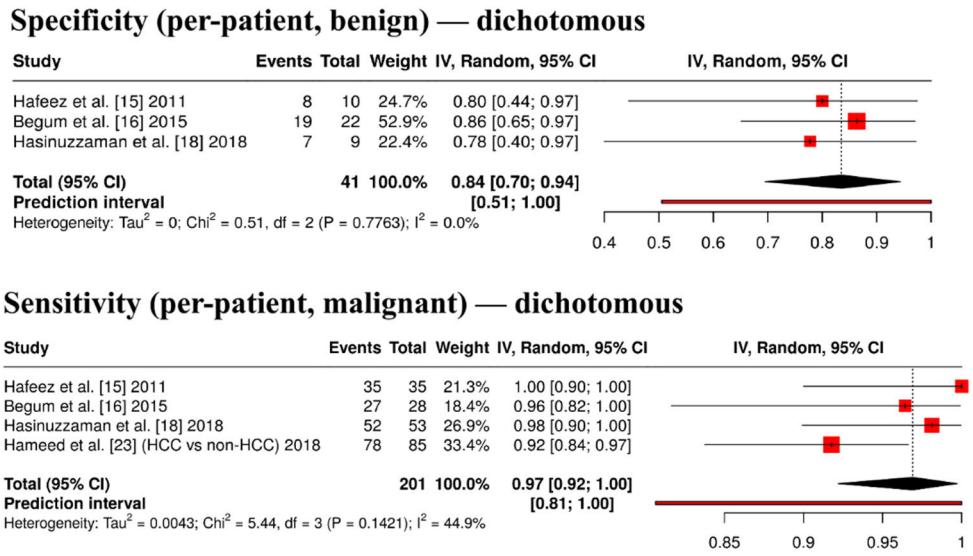

Figure 6: Sensitivity and Specificity Observed

Table 4: GRADE Assessment Observations

Study Design	Number of Studies	Consistent Diagnostic Findings	Risk of Bias	Inconsistency	Indirectness	Imprecision	Additional Factors	Overall Certainty
Prospective Cross-sectional	4 (incl. [15], [19], [23], [25])	Consistently reported high sensitivity and overall accuracy in distinguishing benign vs malignant liver lesions, though with some variability in specificity	Low	Low to moderate	Low	Low	Minor risk of overdiagnosis in cirrhotic livers	High
Cross-sectional (Multicenter/Other)	3 (incl. [16], [17], [18])	Maintained good diagnostic balance between sensitivity and specificity across varying lesion types and sizes	Low	Low	Low	Low	Well-defined pathology endpoints	High
Retrospective Cohort	2 (incl. [20], [22])	Showed high diagnostic accuracy using CT-based modeling; models were validated but based on resected lesions only	Low to moderate	Low	Low to moderate	Low to moderate	Lacked real-time diagnostic generalizability	Moderate
Prospective Observational	1 ([21])	Demonstrated strong lesion characterization but slightly lower sensitivity for small HCC lesions	Low	Moderate	Low	Moderate	Limited lesion verification in small nodules	Moderate
Observational Cross-sectional	1 ([24])	Displayed limited diagnostic reliability for atypical HCC without classical imaging features	Low to moderate	Moderate	Moderate	Moderate	High false-negative rate; reliance on biopsy for confirmation	Moderate

Sensitivity and Specificity

Sensitivity was 0.97 (95% CI: 0.92-1.00) with moderate heterogeneity (I^2 = 44.9%), likely due to variation in population characteristics and malignancy subtypes between studies (e.g., hepatocellular carcinoma-specific and mixed malignancy cohorts) (Figure 6). All four studies (including Hameed *et al.* [23]) had high sensitivity, ranging from 92% to 100%. However, specificity was more relative with a pooled estimate of 0.84 (95% CI: 0.70-0.94) and broader confidence and prediction intervals, though without heterogeneity (I^2 = 0%). This reflects a relative tendency of triphasic CT to misdiagnose benign lesions, possibly due to overlapping enhancement patterns in chronic liver disease.

GRADE Assessment Observations

Most of the studies reviewed were cross-sectional (single or multicenter) or prospective cross-sectional, which is an adequate design for real-world diagnostic evaluation

without intervention (Table 4). The designs were of high certainty of evidence since they reliably identified malignant lesions with good sensitivity and specificity, utilized confirmatory histopathology and were immediately clinically applicable.

Retrospective cohort study designs, despite their high methodological rigor, expressed only moderate certainty because of the possibility of selection bias, use of resected specimens (preventing generalizability) and the retrospective nature of assessments of the lesions. Similarly, in the same context, the prospective observational study and observational cross-sectional design were also graded as moderate certainty because of problems such as loss of sensitivity to detect small lesions or growing dependency on biopsy when imaging results were unusual.

DISCUSSION

In oncologic clinical staging, i.e., CRLM, triphasic CT protocols-particularly in combination with PET-have proven beneficial for lesion detection and operation planning, though optimization of injection protocols remains necessary to attain maximum lesion-to-liver contrast [26]. Existing evidence has confirmed that multiphasic CT can be sensitive to perfusion-related alterations, e.g., in parenchymal injury, that may mimic neoplastic processes in trauma or inflammatory disease [27]. In this regard, the vascular dynamics of contrast injection-i.e., duration and rate-immediately affect enhancement quality and resultant lesion conspicuity. Experimental research within Multidevice Detector CT (MDCT) platforms has shown that shorter injection durations with higher flow rates yield improved contrast differentials, integral to detection of small or atypically enhancing lesions [28].

Hafeez *et al.* [15], Begum *et al.* [16] and Hasinuzzaman *et al.* [18] yielded results that were virtually similar, highlighting superior sensitivity and excellent overall diagnostic performance. The findings revealed high agreement in conclusions, although there were variations in specificity on account of regenerative nodules that are imitated HCC in cirrhotic livers.

Ahirwar *et al.* [17] and Wu *et al.* [20] agreed with the findings but added a CT-based nomogram with superior discriminatory power, with slight differences in methodological quality and statistical analysis stability. However, its clinical application-i.e., that washout and arterial enhancement patterns are good malignancy indicators-complied with the straightforward diagnostic paradigms cited by other research studies.

Mittal *et al.* [21] reached the same overall conclusion but included decreased sensitivity for small HCCs, postulating that triphasic CT has a limitation in disclosing early malignancies. Musa *et al.* [22] demonstrated overall concurrence with the foregoing, confirming high diagnostic accuracy but with the possibility of interpretive difficulty for unusual benign lesions.

In contrast, Naqvi *et al.* [24] and Zahur *et al.* [25] provided a discordant note. Both recognized that although triphasic CT was generally helpful, unusual morphology of the lesion may result in false-negative results and thus histopathologic correlation would be required. Hameed *et al.* [23], in confirmation of diagnostic utility, had moderate over-diagnosis, most likely due to the influence of cirrhotic background alterations on imaging.

The use of Artificial Intelligence (AI) in software for Computed Tomography (CT) interpretation is opening up new vistas of lesion grading and risk stratification. Deep learning algorithms based on triphasic CT features like arterial enhancement and texture features have shown promising performance values in grading HCC and thus, have an ancillary role to play in precision oncology pipelines [29]. These approaches go with the current efforts to extract radiomic signatures from triphasic CT, which can be utilized to replace or complement conventional qualitative image assessment.

Despite technological progress, triphasic CT is still suboptimal for the detection of infiltrative hepatic disease like Wilson disease or diffuse parenchymal abnormality. In such cases, CT is not functionally specific in the early diagnosis and is mostly reduced to gross morphological evaluation [30]. Spectral CT and virtual noncontrast imaging were suggested as alternatives to minimize contrast load and radiation dose with preservation of diagnostic sensitivity for hepatic metastases [31]. These newer techniques, promising as they are, are not yet institution-wide standard, attesting to the persistence of conventional triphasic protocols.

Hemodynamic parameters, e.g., splenoportal indices and hepatic venous waveforms indicating cirrhotic severity, also affect contrast dynamics and lesion detection using triphasic imaging [32]. Radiomic nomograms based on triphasic scans have similarly been found useful in distinguishing benign adrenal lesions from hepatic metastases, indicating the universality of this imaging technique across organ systems in cancer patient populations [33]. However, the diagnostic value of triphasic CT in some patient populations is questionable. For example, in fatty liver disease-a disease increasingly overlapping with oncologic imaging-the sensitivity of CT for the detection of CRLM drops dramatically and MRI is utilized instead in such situations [34]. Likewise, changes in iodine flow rates have been demonstrated to affect the generation of virtual unenhanced images, sometimes substituted by true non-contrast scans in abdominal CT protocols [35].

Routine CT is also suboptimal according to liver graft steatosis assessment in transplantation, with triphasic imaging having only modest diagnostic agreement with histologic results [36]. Vascular congestion, which is commonly seen in the pre-transplant or post-resection environment, can also obscure arterial phase enhancement, adding to the difficulty of lesion detection [37]. This has generated interest in texture analysis techniques on triphasic imaging, specifically in patients treated with such therapies as Y-90 radioembolization, for which regular response criteria may be inadequate [38].

Interventional uses of triphasic CT have also expanded, particularly in the guidance of ablative treatments like electrochemotherapy for portal vein tumor thrombosis. The capability of triphasic CT to demarcate perfusion margins and necrosis areas allows for accurate targeting of cirrhotic livers [39]. Post-treatment alterations such as calcification or remodeling of the parenchyma, however, can simulate complete response and, hence, lead to misinterpretation if triphasic criteria alone are used [40].

Recent clinical case reports have demonstrated the value of triphasic computed tomography in the detection of uncommon complications, such as hemobilia and uncommon biliary obstructions, especially in the setting of cholecystectomy or trauma [41]. Protocol optimizations, including the employment of triphasic contrast injection and single-pass scanning, have enhanced operational efficiency in trauma units and potentially extend to oncological scanning protocols [42]. In spite of this, side effects such as contrast-induced sialadenitis, however uncommon, have been reported in some instances and must be employed cautiously in predisposed patients [43].

CONCLUSION

Triphasic CT offers a noticeably sensitive and clinically useful approach to characterizing focal liver lesions in cirrhotic patients. Regardless of moderate limitations in specificity owing to lesion and cirrhotic liver anatomy overlap, its non-invasive nature and high predictability made its continued role in algorithms for diagnosis warranted. The modality was useful in assisting in guiding clinical decision-making to further management.

Limitations

Analysis was constrained by heterogeneity of imaging protocol, lesion category and interpretation criteria among trials included. Specificity was invariably lowered in cirrhotics, where regenerative nodules simulated malignancy. An inadequate number of trials were not informative about lesion size and number of lesions per patient in a consistent manner, making the data noncomparable. Some analyses were also constrained by small numbers, retrospective design and lack of blinding on image interpretation.

Recommendations

With the existing evidence, triphasic CT will remain an imaging first-line imaging modality to evaluate focal liver lesions in cirrhotic patients. Imaging findings should be used cautiously with unusual vascular enhancement or background cirrhosis to avoid false positives. Use of standardized reporting systems like LI-RADS and correlation of CT imaging findings with clinical and laboratory information may be useful to increase diagnostic accuracy.

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