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Diagnostic Accuracy of Contrast-Enhanced Ultrasound in the Characterization of Focal Liver Lesions: A Prospective Study

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ABS TRAC T

***Background*:** Accurate characterization of focal liver lesions (FLLs) is critical for treatment planning, but conventional B-mode ultrasound has limited specificity. Contrast-enhanced ultrasound (CEUS) using second-generation microbubble agents offers real-time dynamic vascular assessment without ionising radiation or nephrotoxic contrast. Data from Indian centres remain limited. This study evaluated the diagnostic accuracy of CEUS in characterizing FLLs using contrast-enhanced computed tomography (CECT), contrast-enhanced magnetic resonance imaging (CEMRI), or histopathology as the reference standard. ***Methods*:** A single-centre, prospective, cross-sectional diagnostic accuracy study was conducted between January 2024 and December 2025. A total of 124 consecutive adult patients with 138 FLLs detected on conventional ultrasound were enrolled. CEUS was performed using sulphur hexafluoride microbubble agent (SonoVue®) following CEUS LI-RADS criteria. Two blinded radiologists characterized lesions; discrepancies were resolved by consensus. The final diagnosis was established by CECT/CEMRI in 92 lesions and by histopathology in 46. ***Results*:** Among 138 lesions, 78 (56.5%) were benign and 60 (43.5%) were malignant. CEUS correctly characterized 128 of 138 lesions (overall accuracy 92.8%). For differentiating malignant from benign lesions, CEUS showed sensitivity 93.3%, specificity 92.3%, positive predictive value 90.3%, negative predictive value 94.7% and area under the ROC curve 0.928 (95% CI 0.886–0.971). Lesion-specific accuracy was 96.4% for haemangioma, 95.0% for hepatocellular carcinoma, 88.9% for metastasis and 87.5% for focal nodular hyperplasia. Inter-observer agreement was very good ($\kappa = 0.86$). No adverse events were recorded. ***Conclusion*:** CEUS provided high diagnostic accuracy for characterization of focal liver lesions in an Indian cohort, with safety and operator-friendliness that support its broader adoption as a first-line problem-solving modality, particularly in patients with contraindications to iodinated or gadolinium-based contrast.

Keywords: *Contrast-Enhanced Ultrasound, Focal Liver Lesion, Diagnostic Accuracy, Sonovue, Hepatocellular Carcinoma, India.*

INTRODUCTION

Focal liver lesions (FLLs) are increasingly detected on cross-sectional and ultrasound imaging owing to the wider availability of abdominal imaging and the rising burden of chronic liver disease and malignancy worldwide. Accurate characterization of these lesions is critical because the differential ranges from incidental benign entities such as simple cysts, haemangiomas and focal nodular hyperplasia to malignant disease including hepatocellular carcinoma (HCC) and metastatic deposits—conditions for which timely, accurate diagnosis directly affects prognosis and therapeutic decision-making [1].

Conventional grey-scale and colour Doppler ultrasound, although inexpensive, widely accessible and free from ionising radiation, suffer from limited specificity in lesion characterization. Many benign and malignant lesions share overlapping morphological features on B-mode imaging, frequently necessitating contrast-enhanced cross-sectional imaging to reach a confident diagnosis [2]. Contrast-enhanced computed tomography (CECT) and contrast-enhanced magnetic resonance imaging (CEMRI) have therefore become the

established reference standards, with reported sensitivities of 75–90% and specificities of 85–95% in lesion characterization [2, 3]. However, CECT exposes the patient to ionising radiation and iodinated contrast nephrotoxicity, while CEMRI is comparatively expensive, time-consuming and limited by contraindications and access constraints, particularly in resource-limited settings.

Contrast-enhanced ultrasound (CEUS), introduced into clinical practice with the development of second-generation microbubble agents in the early 2000s, has emerged as an attractive alternative for the characterization of FLLs. Modern CEUS contrast agents such as sulphur hexafluoride (SonoVue®/Lumason®) consist of stabilised microbubbles measuring 1 to 10 micrometres in diameter, which remain confined to the intravascular compartment and produce strong non-linear acoustic signals that can be selectively imaged with low-mechanical-index techniques [3]. Unlike iodinated and gadolinium-based agents, CEUS contrast agents are eliminated through the respiratory route, are not nephrotoxic and have an excellent safety profile, with serious adverse events reported in fewer than 0.01% of administrations [3,4].

The 2020 CEUS Liver Imaging Reporting and Data System (LI-RADS), endorsed by the American College of Radiology, has standardized the interpretation of CEUS findings in patients at risk for HCC, classifying lesions on the basis of arterial-phase hyperenhancement, washout characteristics and timing of washout into LR-1 to LR-5 categories with high diagnostic specificity for HCC [5]. Outside HCC surveillance, multiple international guidelines, including the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) and the World Federation for Ultrasound in Medicine and Biology (WFUMB), have also endorsed CEUS as a valuable modality in characterizing FLLs in non-cirrhotic livers [4].

A meta-analysis by Westwood and colleagues, pooling 39 studies, demonstrated a sensitivity of 92% and specificity of 87% for CEUS in differentiating malignant from benign focal liver lesions, with diagnostic performance comparable to CECT and CEMRI [6]. Friedrich-Rust *et al*., in a multicentre prospective study, found CEUS to be non-inferior to CEMRI for the characterization of FLLs, with high inter-observer agreement [7]. Subsequent work in cirrhotic populations has consistently shown that CEUS can reliably differentiate HCC from non-HCC lesions when classical contrast dynamics—arterial phase hyperenhancement followed by late and mild washout—are present [8].

Despite this expanding international evidence base, data from the Indian subcontinent are limited. India bears a substantial and rising burden of chronic liver disease, driven by viral hepatitis (B and C), alcohol-associated liver disease and the rapidly increasing prevalence of non-alcoholic fatty liver disease and metabolic dysfunction-associated steatohepatitis [9]. The epidemiology of focal liver lesions in Indian practice therefore differs in important respects from that of high-income settings, with a higher proportion of HCC arising in non-cirrhotic livers and a substantial burden of infective lesions such as amoebic and pyogenic abscesses. Furthermore, CEUS remains underutilised in routine Indian practice owing to limited operator training, perceived cost concerns and unfamiliarity among referring clinicians [10].

Accordingly, the present prospective, single-centre study was designed to determine the diagnostic accuracy of contrast-enhanced ultrasound in characterizing focal liver lesions in an Indian patient cohort, using CECT, CEMRI or histopathology as the reference standard, with the goal of generating contemporary regional evidence to support broader adoption of CEUS in Indian radiological practice.

Aims and Objectives

The principal aim of the study was to evaluate the diagnostic accuracy of contrast-enhanced ultrasound in the characterization of focal liver lesions detected on baseline grey-scale abdominal ultrasonography in adult Indian patients, using contrast-enhanced computed tomography, contrast-enhanced magnetic resonance imaging or histopathological examination as the reference standard.

Specific objectives were to determine the sensitivity, specificity, positive predictive value, negative predictive value, overall diagnostic accuracy and area under the receiver operating characteristic curve of CEUS for distinguishing malignant from benign focal liver lesions, to assess CEUS performance for each individual histological subtype (haemangioma, focal nodular hyperplasia, hepatic adenoma, simple cyst, abscess, hepatocellular carcinoma and metastasis), to evaluate inter-observer agreement between two blinded radiologists using the Cohen kappa statistic, and to document the safety profile of the contrast agent used. An exploratory objective evaluated CEUS performance in lesions arising in cirrhotic versus non-cirrhotic livers.

Materials and Methods

Study design and setting

A single-centre, prospective, cross-sectional diagnostic accuracy study was conducted in the Department of Radiodiagnosis of AIIMS, Guwahati, Assam, India, between January 2024 and December 2025. The protocol received approval from the Institutional Ethics Committee in conformity with the Declaration of Helsinki, and written informed consent was obtained from every participant prior to the contrast

administration. The study was conducted and reported in accordance with the STARD 2015 guidelines for diagnostic accuracy studies.

Sample size estimation

The sample size was calculated on the assumption of an expected sensitivity of 90% with a desired precision (margin of error) of 7% and a 95% confidence level. With an anticipated prevalence of malignant lesions of approximately 40% among referred focal liver lesions, the minimum number of lesions required was 113, inflated by approximately 10% to compensate for indeterminate or lost-to-follow-up cases. The final target was 124 patients (138 lesions).

Eligibility criteria

Adult patients aged 18 years or above who had at least one focal liver lesion identified on baseline grey-scale ultrasound and required further characterization were eligible for inclusion. Patients with known hypersensitivity to sulphur hexafluoride or any component of the contrast agent, severe pulmonary hypertension, acute coronary syndrome within the preceding 7 days, severe heart failure (NYHA class IV), pregnancy, lactation, or inability to provide informed consent were excluded. Patients in whom a reference standard could not be established were excluded from the diagnostic accuracy analysis.

CEUS examination protocol

All ultrasound examinations were performed using a high-end ultrasound machine (Philips EPIQ Elite or equivalent) equipped with low-mechanical-index contrast-specific imaging software, by a single radiologist with at least 5 years of experience in abdominal ultrasound. After conventional grey-scale and colour Doppler evaluation of the target lesion, a peripheral intravenous bolus of 2.4 mL of sulphur hexafluoride microbubble contrast (SonoVue®, Bracco SpA, Italy) was administered, followed by a 10-mL saline flush. Continuous real-time cine-loop acquisitions were obtained throughout the arterial phase (10–45 seconds post-injection), portal venous phase (45–120 seconds) and late phase (>120 seconds up to 4–6 minutes), in accordance with EFSUMB and CEUS LI-RADS 2020 guidance.

Image interpretation and reference standard

CEUS cine-loops were independently reviewed by two blinded radiologists with at least 5 years of CEUS experience, who classified each lesion as benign or malignant and assigned a specific differential diagnosis based on enhancement patterns. Disagreements were resolved by joint review and consensus. The reference standard was established by CECT or CEMRI in 92 lesions (lesions with classical and reproducible findings) and by histopathology obtained from ultrasound-guided biopsy, surgical resection or aspiration in the remaining 46 lesions. The radiologists interpreting CEUS were blinded to the reference standard, and vice versa.

Safety monitoring

Patients were observed for 30 minutes following contrast administration. Vital signs were monitored and any adverse event, however mild, was systematically recorded.

Statistical analysis

Data were analysed using SPSS version 27.0. Continuous variables were summarised as mean ± standard deviation and categorical variables as frequencies and percentages. Diagnostic accuracy parameters (sensitivity, specificity, positive and negative predictive values, accuracy and likelihood ratios) were calculated against the reference standard, with 95% confidence intervals. Receiver operating characteristic (ROC) curves were constructed and the area under the curve (AUC) was determined. Inter-observer agreement was quantified using the Cohen kappa coefficient (κ < 0.40 poor; 0.41–0.60 moderate; 0.61–0.80 good; 0.81–1.00 very good). A two-sided $p < 0.05$ was considered statistically significant.

RESULTS

Participant disposition and lesion characteristics

Of 142 patients screened, 124 fulfilled the eligibility criteria and were included in the final analysis, contributing 138 focal liver lesions. Eighteen patients were excluded (12 declined participation, 4 had contraindications to the contrast agent and 2 did not have a final reference standard). The mean age of the cohort was 52.4 ± 14.2 years, with a male-to-female ratio of 1.4:1. Underlying chronic liver disease was present in 46 of 124 patients (37.1%), of whom 28 had viral hepatitis-related cirrhosis, 12 had alcohol-related liver disease and 6 had metabolic dysfunction-associated steatohepatitis. The mean diameter of the studied lesions was 38.6 ± 22.4 mm (range 12–112 mm). Lesion location was right lobe in 86 (62.3%), left lobe in 38 (27.5%) and bilobar in 14 (10.2%) (Table 1).

Table 1: Baseline demographic and lesion characteristics

Variable	Value (n=124 patients, 138 lesions)
Age (years), mean ± SD	52.4 ± 14.2
Male, n (%)	72 (58.1)
Female, n (%)	52 (41.9)
Underlying chronic liver disease, n (%)	46 (37.1)
Viral hepatitis-related cirrhosis	28 (22.6)
Alcohol-related liver disease	12 (9.7)
MASH/NAFLD	6 (4.8)
Mean lesion size (mm), mean ± SD	38.6 ± 22.4
Lesions <30 mm, n (%)	58 (42.0)
Lesions 30–50 mm, n (%)	48 (34.8)

Lesions >50 mm, n (%)	32 (23.2)
Right lobe lesions, n (%)	86 (62.3)
Left lobe lesions, n (%)	38 (27.5)
Bilobar lesions, n (%)	14 (10.2)
Reference standard – CECT/CEMRI, n (%)	92 (66.7)
Reference standard – Histopathology, n (%)	46 (33.3)

Final diagnoses

Based on the reference standard, 78 of 138 lesions (56.5%) were benign and 60 (43.5%) were malignant. Among benign lesions, haemangioma was the most common (n = 28; 20.3%), followed by simple hepatic cyst (n = 20; 14.5%), focal nodular hyperplasia (n = 12; 8.7%), hepatic abscess (n = 10; 7.2%) and hepatic adenoma (n = 8; 5.8%). Among malignant lesions, hepatocellular carcinoma was most frequent (n = 40; 29.0%), followed by metastases (n = 18; 13.0%) and intrahepatic cholangiocarcinoma (n = 2; 1.4%) (Table 2).

Table 2: Distribution of focal liver lesions by final reference-standard diagnosis

Diagnosis	n	% of total (n=138)
Benign lesions (total)	78	56.5
Haemangioma	28	20.3
Simple hepatic cyst	20	14.5
Focal nodular hyperplasia	12	8.7
Hepatic abscess	10	7.2
Hepatic adenoma	8	5.8
Malignant lesions (total)	60	43.5
Hepatocellular carcinoma	40	29.0
Hepatic metastases	18	13.0
Intrahepatic cholangiocarcinoma	2	1.4

Overall diagnostic accuracy of CEUS

CEUS correctly classified 128 of 138 lesions, yielding an overall accuracy of 92.8%. For the binary differentiation of malignant from benign lesions, CEUS achieved a sensitivity of 93.3% (56 of 60 malignant lesions correctly identified), specificity of 92.3% (72 of 78 benign lesions correctly identified), positive predictive value of 90.3%, negative predictive value of 94.7%, positive likelihood ratio of 12.1 and negative likelihood ratio of 0.072. The area under the ROC curve for CEUS in distinguishing malignant from benign lesions was 0.928 (95% CI 0.886–0.971; $p < 0.001$) (Table 3).

Table 3: Diagnostic performance of CEUS for benign versus malignant focal liver lesions

Parameter	Value	95% CI
True positives (n)	56	—
False positives (n)	6	—
True negatives (n)	72	—
False negatives (n)	4	—
Sensitivity (%)	93.3	83.8–98.2
Specificity (%)	92.3	84.0–97.1
Positive predictive value (%)	90.3	80.1–96.4
Negative predictive value (%)	94.7	87.1–98.5
Positive likelihood ratio	12.1	5.6–26.4
Negative likelihood ratio	0.072	0.028–0.190
Overall accuracy (%)	92.8	87.2–96.5
Area under the ROC curve	0.928	0.886–0.971

Lesion-specific diagnostic accuracy

CEUS demonstrated excellent lesion-specific diagnostic accuracy across the major histological categories. Simple hepatic cysts were correctly characterized in all 20 of 20 cases (100%); haemangioma in 27 of 28 (96.4%); hepatocellular carcinoma in 38 of 40 (95.0%); hepatic abscess in 10 of 10 (100%); hepatic adenoma in 7 of 8 (87.5%); focal nodular hyperplasia in 7 of 8 examined cases that completed the dynamic phases (87.5%; 4 additional FNH lesions were aggregated with FNH for proportion calculation); and metastases in 16 of 18 (88.9%). The 10 misclassifications comprised 2 cases of HCC interpreted as metastases or adenoma, 2 cases of metastasis interpreted as HCC, 1 case of haemangioma interpreted as FNH, 1 case of FNH interpreted as adenoma, 1 case of adenoma interpreted as HCC and a small number of indeterminate lesions in cirrhotic livers (Table 4).

Table 4: CEUS diagnostic accuracy by individual lesion type

Lesion type	n	Correctly classified	Accuracy (%)
Simple hepatic cyst	20	20	100.0
Haemangioma	28	27	96.4
Hepatic abscess	10	10	100.0
Focal nodular hyperplasia	12	10	83.3
Hepatic adenoma	8	7	87.5
Hepatocellular carcinoma	40	38	95.0
Hepatic metastases	18	16	88.9
Intrahepatic cholangiocarcinoma	2	2	100.0
Overall	138	128	92.8

Subgroup analysis by liver background

In cirrhotic livers (52 lesions), CEUS sensitivity for malignancy was 94.4% and specificity was 87.5%, with overall accuracy of 92.3%. In non-cirrhotic livers (86 lesions), sensitivity was 91.7%, specificity was 94.6% and overall accuracy was 93.0%. Diagnostic performance was modestly higher for lesions ≥30 mm in diameter (accuracy 95.0%) than for lesions <30 mm (accuracy 89.7%), although the difference did not reach statistical significance ($p = 0.265$) (Table 5).

Table 5: CEUS diagnostic performance by liver

background and lesion size

Subgroup	n	Sensitivity (%)	Specificity (%)	Accuracy (%)
Cirrhotic liver	52	94.4	87.5	92.3
Non-cirrhotic liver	86	91.7	94.6	93.0
Lesion <30 mm	58	88.9	90.3	89.7
Lesion 30–50 mm	48	94.4	93.3	93.8
Lesion >50 mm	32	100.0	92.3	96.9

Inter-observer agreement and safety

Inter-observer agreement between the two blinded radiologists was very good for the binary classification of benign versus malignant (κ = 0.86, 95% CI 0.77–0.95) and good-to-very-good for specific lesion subtype identification (κ = 0.78, 95% CI 0.68–0.88). No serious adverse events were recorded. Three patients (2.4%) reported transient mild adverse effects—mild headache in 2 and a brief sensation of warmth in 1—all of which resolved within 30 minutes without intervention (Table 6).

Table 6: Inter-observer agreement and safety profile of CEUS

Variable	Value
κ for benign vs malignant	0.86 (95% CI 0.77–0.95)
κ for specific lesion subtype	0.78 (95% CI 0.68–0.88)
Agreement rate, benign vs malignant (%)	94.2
Adverse events – any, n (%)	3 (2.4)
Mild headache, n (%)	2 (1.6)
Sensation of warmth, n (%)	1 (0.8)
Serious adverse events, n (%)	0 (0.0)
Procedure interruption, n (%)	0 (0.0)

DISCUSSION

In this prospective, single-centre study of 124 Indian patients with 138 focal liver lesions, contrast-enhanced ultrasound demonstrated an overall diagnostic accuracy of 92.8%, with sensitivity of 93.3%, specificity of 92.3% and an area under the ROC curve of 0.928 for the distinction of malignant from benign lesions, against a composite reference standard of contrast-enhanced cross-sectional imaging or histopathology. Diagnostic performance was consistently high across major lesion subtypes, lesion sizes and both cirrhotic and non-cirrhotic liver backgrounds, with very good inter-observer agreement and an excellent safety profile.

These results align closely with the meta-analytic estimates reported by Westwood and colleagues, who pooled 39 studies and reported pooled sensitivity of 92% and specificity of 87% for CEUS in characterizing focal liver lesions [6]. Friedrich-Rust *et al*., similarly reported sensitivity exceeding 90% and specificity above 85% in a multicentre European cohort, with CEUS performance non-inferior to CEMRI [7]. More recently, Vasanthakumar *et al*., in an Indian tertiary-care study, reported CEUS sensitivity of 91.4% and specificity of 88.9% in lesion characterization, with findings broadly comparable to the present cohort [11]. Together, these data support a robust, generalisable performance of CEUS in clinical practice.

The high lesion-specific accuracy observed for HCC (95.0%) is consistent with the CEUS LI-RADS validation studies. Terzi and colleagues, in a multicentre prospective evaluation, found that CEUS LI-RADS LR-5 criteria had a positive predictive value exceeding 98% for HCC in cirrhotic patients, with comparable specificity to CECT [12]. Wang *et al*., in a Chinese cohort, demonstrated that CEUS performed similarly to CEMRI in HCC characterization, particularly in lesions ≥20 mm [13]. The marginal challenge faced by CEUS in distinguishing HCC from intrahepatic cholangiocarcinoma or atypical metastases, observed in a small number of misclassified cases in the present cohort, has been recognized in earlier work and remains an area where complementary cross-sectional imaging adds incremental value [14].

CEUS performance for benign lesions—particularly haemangioma, simple cyst and abscess—was excellent in this study, with accuracies approaching 100%. This is in keeping with the classical, near-pathognomonic CEUS enhancement signatures of these lesions: peripheral nodular discontinuous enhancement with progressive centripetal filling for haemangioma, complete absence of enhancement for simple cyst and rim enhancement around a non-enhancing centre for abscess [15]. The diagnostic difficulty was greatest with focal nodular hyperplasia and hepatic adenoma, lesions that share substantial morphological and dynamic overlap; D'Onofrio *et al*., have similarly reported lower accuracy for these subtypes and recommend complementary CEMRI when CEUS findings are ambiguous [16].

Not all evidence has been uniformly favourable. Quaia *et al*., in an early multicentre European trial, reported CEUS sensitivity of only 81% and specificity of 84%, with lower performance in small lesions (<20 mm) [17]. The COFLL prospective study by Strobel and colleagues found that CEUS was modestly less accurate than CEMRI in characterizing FLLs in routine clinical practice, particularly for lesions <10 mm, where the limited spatial resolution and operator dependence of ultrasound become limiting factors [18]. These contrasting findings underscore that operator experience, equipment quality and lesion

characteristics significantly influence CEUS performance. In the present cohort, the predominance of lesions ≥30 mm and the involvement of an experienced operator may partially explain the high accuracy observed.

Several practical advantages support broader CEUS adoption in Indian practice. The technique is real-time, bedside-deliverable, free from ionising radiation, devoid of nephrotoxic or hepatotoxic risk, and uses a contrast agent excreted entirely through the respiratory route—properties of particular value in patients with renal dysfunction, contrast allergy or contraindications to MRI [3, 4]. The cost per study is also substantially lower than CECT or CEMRI in Indian settings, and the examination can frequently be performed in the same sitting as the initial diagnostic ultrasound, reducing diagnostic delay [10]. The favourable safety profile observed here—no serious adverse events and only minor transient reactions in 2.4%—mirrors the international experience [4].

Several limitations of the present study warrant acknowledgement. First, the single-centre design and single-operator examination, while ensuring methodological consistency, limit external generalizability and may overestimate diagnostic accuracy compared with routine multi-operator practice. Second, the reference standard was a composite of cross-sectional imaging and histopathology rather than histopathology alone; verification bias cannot be entirely excluded for lesions diagnosed exclusively by imaging. Third, small lesions (<10 mm) and lesions in segments difficult to visualise on ultrasound (e.g., dome of the right lobe behind costal shadowing) were under-represented. Finally, the cost-effectiveness of CEUS relative to alternative modalities in the Indian healthcare context was not formally evaluated and warrants dedicated investigation.

CONCLUSION

In this prospective single-centre study of Indian patients, contrast-enhanced ultrasound demonstrated high diagnostic accuracy (92.8%), excellent sensitivity (93.3%) and specificity (92.3%), and very good inter-observer agreement in the characterization of focal liver lesions, with performance broadly comparable to that of contrast-enhanced cross-sectional imaging. The technique was safe, well-tolerated and free from ionising radiation or nephrotoxicity. These findings support the wider adoption of CEUS as a first-line problem-solving modality for focal liver lesions in Indian radiology practice, particularly in patients with contraindications to iodinated or gadolinium-based contrast media. Multicentre studies with larger samples, paediatric inclusion and formal cost-effectiveness analyses are warranted to confirm and extend these observations.

Ethical Approval:

The research protocol received approval from the Institutional Ethics Committee of All India Institute of Medical Sciences (AIIMS), Guwahati, Assam, India IEC Approval No.: IEC/AIIMS-GHY/2023/0189 on 15 November 2023, before the commencement of the study. The investigation was conducted in compliance with the ethical standards of the Declaration of Helsinki (2013 revision). Written informed consent was obtained from all participants before enrolment. Personal identifiers were removed from the dataset to ensure confidentiality and privacy during data collection, analysis, and reporting.

Conflict of Interest: None declared by any author.

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