International Journal of Health Sciences and Research
[Indexed, Peer-Reviewed Journal]
Volume 16; Issue: 7; July 2026
Website: www.ijhsr.org
Original Research Article *ISSN: 2249-9571*

Evaluation of Focal Hepatic Lesions on Tissue Harmonic Imaging and Conventional Sonography Along with Histopathological Correlation

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DOI: https://doi.org/10.52403/ijhsr.20260701

ABSTRACT

Background: Focal hepatic lesions span a wide spectrum from benign incidental findings to aggressive malignancies, and accurate characterisation is essential for management. Conventional grayscale ultrasonography is the usual first-line modality but is limited by artefacts, low signal-to-noise ratio and poor margin delineation. Tissue harmonic imaging (THI) reconstructs images from harmonic signals generated within tissue, potentially improving image quality. This study compared THI with conventional ultrasonography and assessed its diagnostic performance against histopathology.

Materials and Methods: In this prospective observational study, 80 patients with focal hepatic lesions underwent paired conventional ultrasonography and THI. Lesion conspicuity, margin definition, artefact burden, signal-to-noise ratio, posterior acoustic enhancement, fluid–solid differentiation and overall image quality were graded on an ordinal scale by two observers. Imaging was correlated with histopathology obtained by fine-needle aspiration cytology or biopsy. Paired image-quality scores were compared using the Wilcoxon signed-rank test.

Results: The cohort was predominantly elderly (mean age 62.5 years) and male (67.5%), with multifocal, right-lobe, hypoechoic or heterogeneously hypoechoic lesions predominating. Metastatic disease (47.5%) and hepatocellular carcinoma (38.8%) were the commonest diagnoses. THI was significantly superior for lesion conspicuity, margin definition, artefact suppression, signal-to-noise ratio, posterior acoustic enhancement, fluid–solid differentiation and overall image quality ($p < 0.05$). Against histopathology, THI showed a sensitivity of 85.5%, specificity of 77.8%, positive predictive value of 93.0%, negative predictive value of 60.9% and accuracy of 83.8% (area under the curve 0.816).

Conclusion: Tissue harmonic imaging significantly improves image quality and diagnostic confidence over conventional ultrasonography and should be routinely incorporated into hepatic ultrasound protocols.

Keywords: *Tissue harmonic imaging, Conventional ultrasonography, Focal hepatic lesions, Image quality, Hepatocellular carcinoma, Liver metastases.*

INTRODUCTION

Focal hepatic lesions constitute a diverse group of entities ranging from clinically irrelevant benign findings to aggressive primary and metastatic malignancies, and accurate detection and characterisation are essential for risk assessment, staging and treatment planning.[1] With the increasing use of abdominal imaging for screening, surveillance and evaluation of unrelated complaints, incidental focal liver lesions are now detected in a substantial proportion of studies, creating a need for reliable strategies to distinguish benign from malignant lesions.[2,3] Although benign lesions such as simple cysts and haemangiomas are more common overall, malignant lesions - particularly metastases and hepatocellular carcinoma arising in chronic liver disease - carry significant morbidity and mortality.[4]

Conventional B-mode ultrasonography remains the first-line imaging modality for hepatic evaluation owing to its wide availability, low cost, real-time capability and absence of ionising radiation. However, its performance is limited by operator dependence, low contrast resolution, reverberation and side-lobe artefacts, and reduced conspicuity of small lesions, particularly in obese, steatotic or cirrhotic livers.[5,6] Computed tomography and magnetic resonance imaging provide superior characterisation, and contemporary guidelines from the major liver societies permit non-invasive diagnosis of hepatocellular carcinoma in at-risk patients when lesions demonstrate arterial-phase hyperenhancement with subsequent washout.[7,8,9,10] Nevertheless, these modalities are costlier and less accessible, so improving the diagnostic yield of ultrasound retains considerable clinical value.

Tissue harmonic imaging exploits the non-linear propagation of ultrasound through tissue, in which progressive waveform distortion generates harmonic frequencies - predominantly the second harmonic - that are selectively used for image reconstruction. Because harmonic signals are minimally produced in the near field and outside the main beam axis, reverberation, side-lobe and clutter artefacts are suppressed, while the higher effective frequency improves lateral and contrast resolution. These properties translate into better lesion conspicuity, sharper margins and improved signal-to-noise ratio, with particular benefit in technically difficult patients. [11,12,13]

This study was undertaken to evaluate the effectiveness of tissue harmonic imaging in the assessment of focal hepatic lesions, to compare its image-quality characteristics with those of conventional grayscale ultrasonography, and to determine its diagnostic performance using histopathology as the reference standard.

MATERIALS & METHODS

Study Design and Setting

This prospective observational study was conducted in the Department of Radiodiagnosis and Imaging at our institute over a period of approximately one and a half years (1 August 2024 to 31 December 2025). Ethical approval for the study was obtained from the Institutional Ethics Committee.

Study Population

Patients attending the outpatient and inpatient departments who were referred for ultrasonographic evaluation of suspected focal hepatic lesions were included. Written informed consent was obtained from all participants and patient confidentiality was maintained throughout. The sample comprised 80 eligible patients evaluated during the study period.

Inclusion and Exclusion Criteria

Patients referred for imaging evaluation of suspected focal hepatic lesions were included. Patients with incidentally detected simple hepatic cysts, and those in whom adequate follow-up or histopathological confirmation was not available, were excluded.

Ultrasound Imaging Protocol

Each patient underwent conventional grayscale ultrasonography of the liver

followed by tissue harmonic imaging on the same machine and in the same scanning planes, using a 2–5 MHz curvilinear transducer. Findings were recorded on a predesigned, prevalidated proforma. For every lesion, the conventional and harmonic images were compared for differences in visualisation and image quality.

Image Analysis

Image quality was assessed using a structured, observer-based ordinal grading system adapted from previously published visual grading scales used in comparative studies of tissue harmonic imaging. [6,14,15] The original four- and five-point scales were condensed into a simplified three-point scale to improve reproducibility and reduce inter-observer variability. Lesion conspicuity, margin definition, artefact burden and signal-to-noise ratio were each graded from 1 (poor) to 3 (good). Posterior acoustic enhancement and fluid–solid differentiation were graded as 0 (not demonstrable/assessable), 1 (present/fair) or 2 (better than conventional). Overall image quality was a composite grade from 1 (poor) to 3 (good).

Reference Standard

On both conventional ultrasonography and tissue harmonic imaging, each lesion was additionally categorised as benign or malignant on the basis of standard grayscale and harmonic morphological criteria - margin regularity, internal echotexture and heterogeneity, presence of a peripheral hypoechoic halo, and associated features. This imaging-based categorisation was then compared with the histopathological diagnosis. Diagnostic confirmation was obtained by ultrasound-guided fine-needle aspiration cytology or core-needle biopsy, which served as the reference (gold) standard.

Statistical Analysis

Data were analysed using IBM SPSS Statistics for Windows, version 26.0. Categorical variables were expressed as frequencies and percentages and continuous variables as mean ± standard deviation. Paired image-quality scores on conventional ultrasonography and tissue harmonic imaging were compared using the Wilcoxon signed-rank test. The diagnostic performance of tissue harmonic imaging was assessed against histopathology by calculating sensitivity, specificity, predictive values and accuracy, and a receiver-operating-characteristic (ROC) curve was constructed. A p-value of less than 0.05 was considered statistically significant.

RESULT

A total of 80 patients with focal hepatic lesions were evaluated. The mean age was 62.49±12.70 years (range 32–89 years), with most patients above 50 years of age and a clear male predominance (67.5%). Abdominal pain was the commonest presenting complaint. Multifocal lesions and right-lobe involvement predominated, and most lesions were hypoechoic or heterogeneously hypoechoic, suggesting a preponderance of malignant pathology (Table 1).

Table 1. Demographic, clinical and lesion characteristics (n = 80)

Variable	Category	n (%)
Age group (years)	<40	2 (2.5)
	41–50	11 (13.8)
	51–60	25 (31.3)
	61–70	17 (21.3)
	>70	25 (31.3)
Sex	Male	54 (67.5)
	Female	26 (32.5)
Presenting complaint	Abdominal pain (diffuse)	37 (46.3)
	Abdominal distension	12 (15.0)
	Known malignancy	11 (13.8)
	Other complaints	11 (13.8)

	Weight loss	9 (11.3)
Number of lesions	Single	33 (41.3)
	Multiple	47 (58.8)
Lobe involved	Right lobe	48 (60.0)
	Both lobes	22 (27.5)
	Left lobe	10 (12.5)
Echogenicity pattern	Hypoechoic	32 (40.0)
	Heterogeneously hypoechoic	33 (41.3)
	Heterogeneously hyperechoic	6 (7.5)
	Hyperechoic	5 (6.3)
	Anechoic with internal echoes	4 (5.0)

Mean age 62.49 ± 12.70 years (range 32–89).

On conventional grayscale ultrasonography, image quality was suboptimal across all parameters: lesion conspicuity was only moderate in 82.5% of cases, margins were poorly defined in 85.0%, artefacts were prominent in 81.3%, and the perceived signal-to-noise ratio was poor in 78.8%. Tissue harmonic imaging showed a marked improvement—good lesion conspicuity in 82.5%, no poorly defined margins, no cases with prominent artefacts, and moderate-to-high signal-to-noise ratio in almost all examinations (Table 2; Figures 1 and 2).

Table 2. Image-quality parameters on conventional ultrasonography (USG) versus tissue harmonic imaging (THI) (n = 80)

Parameter	Grade	Conventional USG, n (%)	THI, n (%)
Lesion conspicuity	Poor	6 (7.5)	0 (0.0)
	Moderate	66 (82.5)	14 (17.5)
	Good	8 (10.0)	66 (82.5)
Margin definition	Ill-defined	68 (85.0)	0 (0.0)
	Partially defined	10 (12.5)	75 (93.8)
	Well defined	2 (2.5)	5 (6.3)
Artefact burden	Prominent	65 (81.3)	0 (0.0)
	Mild	15 (18.8)	56 (70.0)
	Minimal	0 (0.0)	24 (30.0)
Signal-to-noise ratio	Poor	63 (78.8)	1 (1.3)
	Moderate	17 (21.3)	67 (83.8)
	High	0 (0.0)	12 (15.0)

Posterior acoustic enhancement and fluid–solid differentiation were not assessable in most cases owing to the predominance of solid lesions; however, in assessable lesions tissue harmonic imaging more frequently demonstrated these features and demonstrated them more clearly than conventional ultrasonography (Table 3; Figures 3 and 4).

Table 3. Posterior acoustic enhancement and fluid–solid differentiation (n = 80)

Parameter	Category	n (%)
Posterior acoustic enhancement – Conventional	Absent	66 (82.5)
	Present	14 (17.5)
Posterior acoustic enhancement – THI	Absent	66 (82.5)
	Present, same as conventional	4 (5.0)
	Better than conventional	10 (12.5)
Fluid–solid differentiation – Conventional	Not assessable	66 (82.5)
	Demonstrable	14 (17.5)
Fluid–solid differentiation – THI	Not assessable	66 (82.5)
	Same as conventional	5 (6.3)
	Better than conventional	9 (11.3)

On paired comparison using the Wilcoxon signed-rank test, tissue harmonic imaging was significantly superior to conventional ultrasonography for every parameter, including overall image quality (Table 4). Among lesions in which posterior acoustic enhancement and fluid–solid differentiation were assessable (n = 14), tissue harmonic imaging was better than conventional ultrasonography in 71.4% and 64.3% of cases respectively, with no case favouring conventional imaging (p = 0.001 and p = 0.008).

Table 4. Paired comparison of image-quality parameters (Wilcoxon signed-rank test)

Parameter	Z value	p-value
Lesion conspicuity	−7.87	<0.001
Margin definition	−8.13	<0.001
Artefact elimination	−4.47	<0.001
Fluid–solid differentiation	−3.61	<0.001
Posterior acoustic enhancement	−2.02	0.043
Perceived signal-to-noise ratio	−2.12	0.034
Overall image quality	−5.57	<0.001

A composite image-quality score derived from the predominant grade of each parameter further confirmed the difference: conventional ultrasonography achieved a total score of 5 (overall poor), whereas tissue harmonic imaging achieved 9 (overall fair) (Table 5).

Table 5. Composite image-quality score – conventional ultrasonography versus tissue harmonic imaging

Parameter	Conv. grade	Conv. score	THI grade	THI score
Lesion conspicuity	Fair	2	Good	3
Margin definition	Poor	1	Fair	2
Artefact elimination	Poor	1	Fair	2
Signal-to-noise ratio	Poor	1	Fair	2
Total score	—	5	—	9
Overall image quality	—	Poor	—	Fair

Diagnostic confirmation was obtained by fine-needle aspiration cytology in 67.5% of patients and by core-needle biopsy in 32.5%. Metastatic liver disease was the commonest final diagnosis (47.5%), followed by hepatocellular carcinoma (38.8%); benign and infective lesions and cholangiocarcinoma formed the remainder (Table 6).

Table 6. Mode of confirmation and final diagnosis (n = 80)

Category	Sub-group	n (%)
Mode of confirmation	Fine-needle aspiration cytology	54 (67.5)
	Core-needle biopsy	26 (32.5)
Final diagnosis	Metastatic liver disease	38 (47.5)
	Hepatocellular carcinoma	31 (38.8)
	Benign / infective lesions	7 (8.7)
	Cholangiocarcinoma	4 (5.0)

Compared with histopathology, tissue harmonic imaging correctly classified 53 of 62 malignant lesions and 14 of 18 benign lesions. This corresponded to a sensitivity of 85.5%, specificity of 77.8%, positive predictive value of 93.0%, negative predictive value of 60.9% and overall accuracy of 83.8% (Table 7). The ROC curve demonstrated good discriminatory ability, with an area under the curve of 0.816 (p < 0.001) (Figure 5).

Table 7. Diagnostic performance of tissue harmonic imaging against histopathology (n = 80)

THI diagnosis	Histo. malignant	Histo. benign	Total
Malignant	53	4	57
Benign	9	14	23
Total	62	18	80

Diagnostic accuracy measures: *Sensitivity 85.5%, Specificity 77.8%, Positive predictive value 93.0%, Negative predictive value 60.9%, Accuracy 83.8%, Area under the ROC curve 0.816 ($p < 0.001$).*

Figure 1: A 61-year-old obese woman (body mass index 38 kg/m²) with known gastric malignancy and hepatic metastases. (A) Conventional ultrasonography shows a heterogeneously hypoechoic lesion in segment IV with indistinct margins, and adjacent smaller lesions that are obscured by prominent artefacts and poor contrast against the fatty hepatic parenchyma. (B) Tissue harmonic imaging shows sharper lesion margins, clearer delineation of the additional smaller lesions, and improved overall image quality through reduction of side-lobe and reverberation artefacts, reduced speckle and improved signal-to-noise ratio. Fine-needle aspiration cytology confirmed metastatic adenocarcinoma.

(A) Conventional ultrasonography

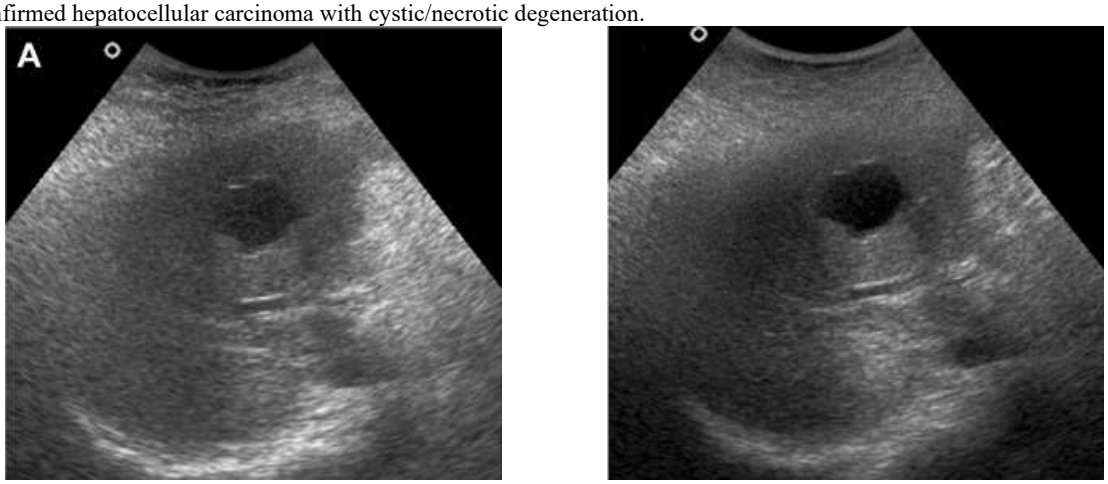
(B) Tissue harmonic imaging

Figure 2: A 68-year-old woman with abdominal distension and known colorectal carcinoma. (A) Conventional ultrasonography shows a large (7.5 cm) heterogeneous lesion in the right lobe with poorly defined margins, internal hypoechoic areas suggestive of necrosis and only subtle posterior acoustic enhancement. (B) Tissue harmonic imaging shows improved lesion conspicuity, better margin delineation, clearer depiction of the internal necrotic/cystic components and more conspicuous posterior acoustic enhancement. Fine-needle aspiration cytology confirmed metastatic adenocarcinoma with necrosis.

(A) Conventional ultrasonography

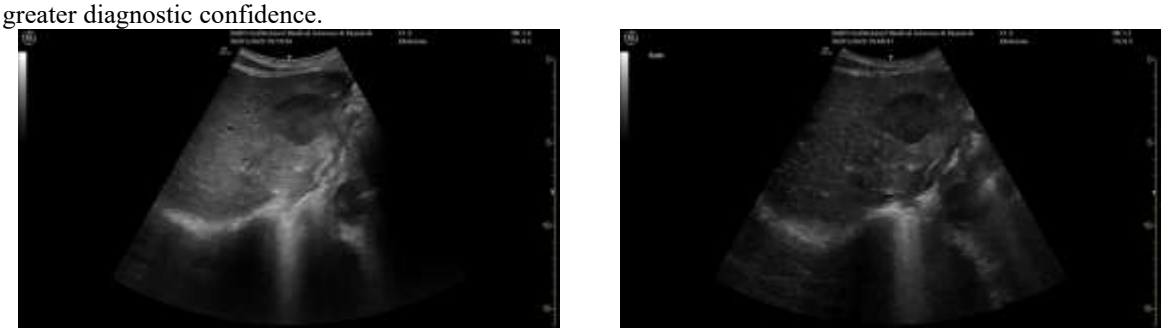
(B) Tissue harmonic imaging

Figure 3: A 55-year-old man with chronic hepatitis C and hepatocellular carcinoma. (A) Conventional ultrasonography shows a complex cystic lesion in segment VII with ill-defined margins, subtle internal echoes and barely discernible posterior acoustic enhancement obscured by artefacts. (B) Tissue harmonic imaging shows superior fluid–solid differentiation, with clearer depiction of the internal architecture and sharper posterior acoustic enhancement. Biopsy confirmed hepatocellular carcinoma with cystic/necrotic degeneration.



(A) Conventional ultrasonography **(B) Tissue harmonic imaging**

Figure 4: A 58-year-old man with right hypochondrial pain and weight loss. (A) Conventional ultrasonography shows a relatively well-defined, heterogeneously hypoechoic lesion with a suggestion of an internal cystic component and slight posterior enhancement, giving the impression of a cystic lesion; artefacts were prominent with reduced overall image quality. (B) Tissue harmonic imaging shows the same lesion with improved margins, a solid internal architecture and no posterior enhancement, consistent with a solid lesion and allowing greater diagnostic confidence.



(A) Conventional ultrasonography **(B) Tissue harmonic imaging**

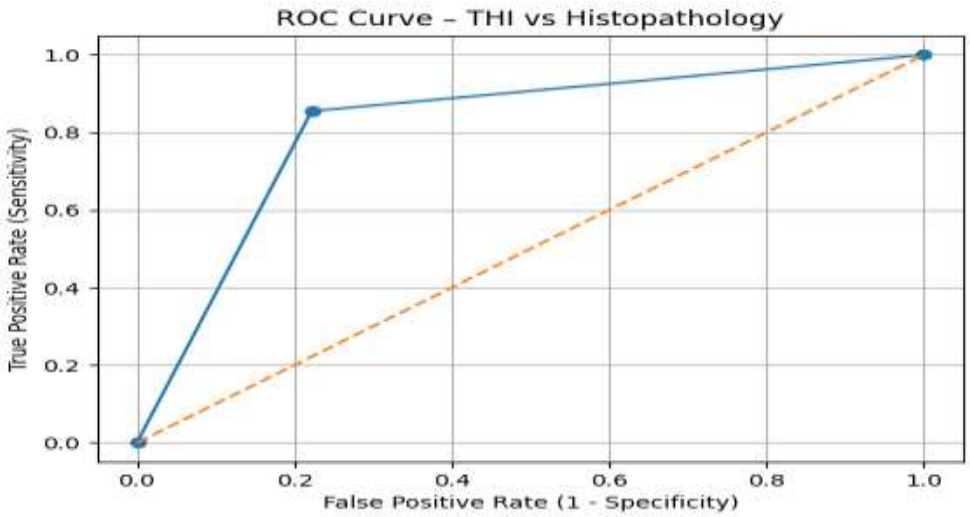


Figure 5: Receiver-operating-characteristic curve showing the diagnostic performance of tissue harmonic imaging for differentiating malignant from benign focal hepatic lesions (area under the curve 0.816).

DISCUSSION

Focal hepatic lesions encompass a broad spectrum of benign and malignant pathology, and their accurate detection and characterisation directly influence staging, treatment and prognosis. Conventional grayscale ultrasonography, though widely used as the initial modality, is constrained by artefacts, low signal-to-noise ratio and poor margin delineation. Tissue harmonic imaging overcomes several of these limitations by reconstructing images from harmonic signals generated within tissue. The present study evaluated this advantage in a clinical cohort and correlated imaging with histopathology.

The cohort was predominantly elderly (mean age 62.5 years) with a male preponderance (67.5%), comparable to earlier descriptions of focal hepatic lesions. Thimmaiah reported a mean age of 55 years with male predominance and a 2:1 male-to-female ratio,[16] and an Indian fine-needle aspiration series similarly found the highest incidence in older men, who accounted for most cases of hepatocellular carcinoma.[17] Abdominal pain was the commonest presenting complaint (46.3%), consistent with Sylviya et al., who reported pain in 92% of patients, and with Thimmaiah and with Ranjan and Singh.[16,18,19] Multifocal involvement predominated (58.8%), differing from series reporting solitary-lesion predominance and reflecting the high proportion of malignant disease in our cohort; multifocality is recognised as a feature of advanced hepatocellular carcinoma and metastatic disease.[20] Right-lobe predominance (60.0%) accorded with the known hepatic vascular anatomy and with previous reports.[16,19,21] Hypoechoic and heterogeneously hypoechoic patterns together accounted for 81.3% of lesions, mirroring Ahmed et al., who reported an almost identical proportion and an association between hypoechogenicity and malignancy.[22]

Conventional ultrasonography demonstrated suboptimal image quality across all parameters in our study, in keeping with Ranga et al. and Oktar et al., who found conventional sonography to yield the lowest scores for lesion conspicuity, margin clarity and artefact suppression, and with Choudhry et al., who reported inferior image quality and lower signal-to-noise ratio with conventional imaging, particularly in patients with poor acoustic windows.[6,12,15] Posterior acoustic enhancement was absent and fluid–solid differentiation was not assessable in more than 80% of cases, reflecting the preponderance of solid lesions; Sodhi et al. similarly noted the limited ability of conventional imaging to resolve internal architecture in heterogeneous lesions.[23]

In contrast, tissue harmonic imaging improved every image-quality parameter. Good lesion conspicuity was achieved in 82.5% of cases and no lesion remained poorly marginated, consistent with reports of improved conspicuity and margin delineation with harmonic techniques.[6,24] Artefacts were reduced to mild or minimal levels in all cases, in line with Oktar et al., and the perceived signal-to-noise ratio improved, as expected from the selective reception of tissue-generated harmonics and as reported by Yen et al.[15,25] In the subset of assessable lesions, harmonic imaging also improved posterior acoustic enhancement and fluid–solid differentiation, supporting earlier observations by Singh et al. and Sodhi et al.[23,24]

On paired statistical comparison, tissue harmonic imaging was significantly superior to conventional ultrasonography for all parameters ($p < 0.05$), with the most pronounced gains in lesion conspicuity and margin definition. These findings concur with Oktar et al. and Ranga et al., who established conventional sonography as the least effective technique, and with Choudhry et al. for artefact reduction and signal-to-noise ratio.[6,12,15] The relatively smaller, though still significant, effect for posterior acoustic enhancement is attributable to the predominance of solid lesions, in which posterior acoustic phenomena are inherently limited.[6] Composite scoring reinforced these results, with conventional imaging

scoring in the poor range and harmonic imaging in the fair range, comparable to the score distributions reported by Oktar et al. and Ranga et al.[6,15]

Fine-needle aspiration cytology was the principal mode of confirmation (67.5%), reflecting routine practice; its accuracy is well established, with Swamy et al. and Gupta et al. reporting diagnostic accuracies of approximately 98% for image-guided sampling of hepatic lesions.[26,27] Metastatic disease was the commonest final diagnosis, followed by hepatocellular carcinoma, paralleling Dash et al. and the Indian fine-needle aspiration series of Kamal and Kumar and underscoring the high burden of advanced hepatic malignancy in hospital populations.[17,28]

Against histopathology, tissue harmonic imaging showed high sensitivity (85.5%) and accuracy (83.8%) with a high positive predictive value (93.0%), indicating strong reliability in confirming malignancy, while the lower negative predictive value (60.9%) reflects limited ability to exclude malignancy confidently. These results are consistent with Tanaka et al., who reported improved lesion detection and characterisation with harmonic imaging, with Sodhi et al., and with harmonic imaging–based studies reporting good performance in differentiating malignant liver lesions. [23,29,30] The improved diagnostic performance follows directly from the enhanced conspicuity, margin delineation and artefact reduction afforded by harmonic imaging, which are especially valuable for small or ill-defined lesions. As a rapid, non-invasive and cost-effective technique requiring no additional contrast or radiation, tissue harmonic imaging is well suited as a first-line tool, particularly in resource-limited settings, with advanced cross-sectional imaging reserved for indeterminate cases.

Formal inter-method agreement was not assessed as a primary outcome; because tissue harmonic imaging systematically upgraded image-quality grades, the paired Wilcoxon signed-rank test provided the appropriate basis for comparison.

Limitations

This was a single-centre study with a modest sample size (n = 80), which may limit generalisability. The predominance of solid and malignant lesions reduced the number of cystic lesions available for assessment of posterior acoustic enhancement and fluid–solid differentiation. Image-quality grading was subjective and observer-dependent, and a formal inter-observer variability (kappa) analysis between independent observers was not performed. Correlation with computed tomography or magnetic resonance imaging was not uniformly available in all cases. Larger, multicentre studies with lesion-specific subgroup analysis, and evaluation of harmonic imaging in combination with compound and contrast-enhanced ultrasound, are recommended to define the optimal ultrasound strategy for focal hepatic lesions.

CONCLUSION

Tissue harmonic imaging is superior to conventional grayscale ultrasonography in the evaluation of focal hepatic lesions, providing significant improvements in lesion conspicuity, margin definition, artefact suppression and signal-to-noise ratio, and thereby enhancing overall image quality and diagnostic confidence. These benefits are achieved without additional time, contrast or radiation. Tissue harmonic imaging also demonstrated good diagnostic performance, with high sensitivity for malignant lesions and good overall accuracy when correlated with histopathology. While it does not replace computed tomography or magnetic resonance imaging for definitive characterisation, tissue harmonic imaging should be considered an essential enhancement to conventional ultrasonography and routinely incorporated into hepatic ultrasound protocols, particularly in patients with poor acoustic windows.

Declaration by Authors:

All the authors have read and approved the submitted version and have agreed both to be

personally accountable for their contributions and to ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethical Approval: Approved by the Institutional Ethics Committee.

Acknowledgement: None

Source of Funding: None

Conflict of Interest: The authors declare no conflict of interest.

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How to cite this article: Ashwanth Manoharan, Deepti Naik, Arvinder Singh. Evaluation of focal hepatic lesions on tissue harmonic imaging and conventional sonography along with histopathological correlation. *Int J Health Sci Res.* 2026; 16(7):1-11. DOI: *https://doi.org/10.52403/ijhsr.20260701*

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