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Role of Ultrasound Elastography in Characterization of Focal Solid Hepatic Lesion

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Abstract
Purpose: Analysis of focal solid hepatic lesions by 2D Shear Wave Sono-Elastography and evaluation of its diagnostic accuracy in differentiating benign from malignant lesions.

Methodology: This study included 58 patients all the studied patients were subjected to grey-scale ultrasound and 2D shear wave sono-elastography which were performed on LOGIQTM P9 XDclearTM (GE Healthcare) ultrasound machine with convex transducer (C1-5-D 3.5 MHz).

Results: Sono-elastography showed that most malignant lesions had higher stiffness (median = 33.4 kPa) and showed mixed colour with red foci, whereas most benign lesions had lower stiffness (median = 13.5 kPa) and showed yellow-green color.

Amongst the malignant lesions, hepatocellular carcinomas showed comparatively lower stiffness values (median = 29.25 kPa) than those of metastases and cholangiocarcinomas (median = 36.65 kPa and 39.3 kPa, respectively), and cholangiocarcinoma was established as the stiffest focal solid hepatic lesion.

Among the benign lesions, focal nodular hyperplasia showed higher stiffness (median = 23.7 kPa). Hemangiomas were comparatively softer lesions; however, they showed higher stiffness values (median = 13.3 kPa) as compared to surrounding normal liver parenchyma (median = 4.45 kPa).

Because of the associated diffuse liver fibrosis, hepatocellular carcinomas had the highest stiffness values of background liver parenchyma (median = 11.1 kPa). This, in turn, resulted in a lower lesion/parenchyma stiffness ratio (median = 2.9) in contrast to other malignant lesions (median = 5.7 and 6.3 for metastases and cholangiocarcinoma's, respectively), with values similar to those seen in cases of benign lesions (median = 2.8).

The threshold cut off value to differentiate benign from malignant solid focal hepatic lesions based on their SWE characteristics was assigned as 15.9 kPa. Using this value with the AUC of 0.9545, the ROC analysis resulted in 100% sensitivity, 90.91% specificity, 97.92% positive predictive value (PPV), 100% negative predictive value (NPV), and 98.28% accuracy.

Conclusion: This study has demonstrated that 2D shear wave sono-elastography is a robust technique and is capable of evaluating stiffness changes in the liver associated with solid focal liver lesions, which helps in distinguishing benign from malignant lesions and also in their sub-categorization, i.e., differentiating focal nodular hyperplasia from hemangioma and differentiating hepatocellular carcinoma from cholangiocarcinoma and metastases, with high sensitivity and accuracy. Thus, it can be added to routine grey-scale sonographic examinations for rapid, cost-effective, non-invasive, and non-contrast assessments to aid the diagnosis and further management.

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1. Introduction

Liver is a common neoplastic organ. Clinicians and radiologists struggle to characterize hepatic lesions. It affects patient management and health care expenses. Focal liver lesions, or FLLs, are solitary or multiple masses of aberrant liver tissue that can develop from hepatocytes, mesenchymal tissue, or biliary epithelium or metastasis from extrahepatic malignancies. They range from benign lesions to metastases from original cancers. Benign and malignant lesions can be solid or cystic [1–4]. Most malignant liver tumours are metastases from the colon, stomach, pancreas, breast, or lung. Primary liver cancer (hepatocellular carcinoma) is the fifth most frequent cancer worldwide and the second major cause of mortality in men and the sixth leading cause in women [(5).] Imaging is needed to detect lesions while they are still receptive to medicinal or surgical treatment.

Hemangioma, focal nodular hyperplasia, hepatic adenoma, localized fatty change, inflammatory lesions (sarcoidosis, histoplasmosis), regenerative and dysplastic nodules, lipoma, angiomyolipoma, focal hepatic fibrosis, and hematoma are solid benign FLLs (post-abdominal trauma). Simple cyst, hydatid cyst, liver abscess (pyogenic or amoebic), Caroli's illness, biloma, biliary cystadenoma, and peliosis hepatis are cystic FLLs.

FLLs can be primary (from the liver) or secondary (originating elsewhere like metastases and lymphomas). Except for cystic and necrotic metastases, most malignant liver lesions are solid. Colon, stomach, pancreatic, breast, and lung are common metastasis locations. Hepatocellular carcinoma, cholangiocarcinoma, fibrolamellar carcinoma, hepatoblastomas, and angiosarcomas are primary lesions.

Gray-scale ultrasonography, colour Doppler, MRI, CT, and PET are utilised to diagnose FLLs. Angiography and percutaneous biopsies are invasive.[6]

The widespread use of imaging modalities with an emphasis on non-invasive imaging techniques has increased the detection of incidental FLLs over the last two decades, preventing the unnecessary use of painful biopsy, especially in the diagnosis of benign touch-me-not lesions, reducing the risk of bleeding and anxiety among patients. Liver hemangiomas, the most frequent benign liver tumour, are accurately diagnosed by imaging [7–9]. Characterizing liver tumours and distinguishing benign from malignant lesions is crucial for planning treatment.

Conventional ultrasonography (US) is often used to examine hepatic lesions because it's cost-effective, easily accessible, and radiation-free. Color-Doppler and CEUS help classify FLLs.

CE-CT and CE-MRI can accurately characterise previously discovered lesions but are more expensive and less accessible. Contraindications to iodinated contrast media used in CECT include a high radiation dosage and a history of allergy or renal failure. MRI lacks ionising radiation, and iodinated contrast chemicals can be utilised in MRI. High expenditures and lengthy exams are its biggest downsides.[10]

A core needle percutaneous liver biopsy is the gold standard for separating malignant and benign tumours.

It's invasive and can cause discomfort, anxiety, haemorrhage, and death. Variability in sample limits biopsy's diagnostic value [11, 12].

Shear wave sono-elastography (SWE) is a novel elastographic imaging technique implemented in conventional real-time ultrasound equipment that allows a simple, rapid, cost-effective, and non-invasive quantitative estimation of elasticity within biological tissues using modified software, offering new perspectives in the imaging of focal liver lesions. It assesses a tissue's inherent tendency to revert to its original shape and size following deformation [(13–15)]. Inflammatory and neoplastic processes can alter an organ's parenchymal stiffness. These stiffness assessments help assess isolated liver lesions and distinguish malignant from benign ones. SWE generates shear waves at a tissue focal point, where wave velocity estimates tissue stiffness. It delivers an organ's local kilopascal evaluation (kPa). Its key advantages are reproducibility, operator independence, greater spatial resolution, and quantitative stiffness evaluation without human compression artefacts [16–17]. SWE can be used as an adjuvant to

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conventional ultrasound to differentiate and characterize focal hepatic lesions, aiding in subsequent therapy. [19–21]

Aims and objectives

Aim: To study the usefulness of 2D-Shear Wave Sono-Elastography in the characterization of focal solid hepatic lesions and differentiating benign from malignant lesions.

Objectives: Analysis of focal solid hepatic lesions by grey-scale ultrasound and 2D-Shear Wave Sono-Elastography including SWE color characteristics and stiffness values (in kPa).

Evaluation of differences amongst the elastographic parameters obtained from various focal liver lesions and their background liver parenchyma with an assessment of lesion/parenchyma stiffness ratio by correlating SWE findings with the definitive diagnosis.

Finding a threshold cut-off value of lesion stiffness obtained by SWE (in kPa) to distinguish benign from malignant lesions and assessment of its diagnostic validity by receiver-operator curve (ROC) analysis.

2. Methodology

Study Design:

Thestudywas designed as aprospective analyticalstudy.

Study Period and duration:

The study was conducted over a period of 18 months from January 2020 to June 2021.

Place:

Thestudywasconducted in the department of Radiodiagnosis, Krishna Institute of Medical Sciences and Hospital, Karad, Maharashtra.

Source of data:

Patients referred from various departments who were found to have focal hepatic lesions on conventional imaging modalities were included in the study.

Sample size

The sample size wascalculatedbyBuderer'sformula [69, 70]:

$$n = \frac{Z^2_{1-\frac{\alpha}{2}} \times S_N \times (1 - S_N)}{L^2 \times Prevalence}$$

Where:

n = required sample size,

SN = anticipated sensitivity,

α = specified size of the critical region (1 − α = confidence level),

Z1−α/2 = standard normal deviate corresponding to α, and

L = Relative precision.

On substitution of values as:

Z1−α/2 = 1.96 (95% confidence),

Anticipated sensitivity of the test = 86%,

Prevalence = 5.8%,

1-SN = 1 - 0.86 = 0.14, and

L (Relative precision) = 4%,

Then, n is equal to ~ 48.

Hence, 48 cases were assigned as the minimum sample size.

However, in the 18-months study period, a total number of 58 cases that fulfilled the selection criteria were studied.

Statistical Analysis

The data collected from B-mode abdominal ultrasound studies and 2D-shear wave sono-elastography value results were transferred on Microsoft Windows to R statistics software (version 3.6.0) for statistical analysis.

Quantitative data were summarized by median, mean and standard deviation (SD) values.

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Qualitative data were summarized by frequency and percentage analysis.

Tofindthesignificanceincategoricaldata, the following tests were done:

i. Unpaired T-test: It compares the means or medians of two independent or unrelated groups to determine if there is a significant difference between the two.

ii. Analysis of variance (ANOVA) test: It is used to check if the means or medians of three or more groups are significantly different from each other.Post hoc tests (pair-wise multiple comparisons) were used to determine the significant pair(s) after ANOVA was found significant.

iii. Receiver operator characteristic (ROC) curve analysis was used to determine the diagnostic accuracy of the test. A threshold cut-off value for lesion stiffness (obtained by 2D shear wave sono-elastography in kPa) was selected to obtain the highest sensitivity and specificity. Positive and negative predictive values, as well as efficacy, were calculated to evaluate diagnostic accuracy.

For all above mentioned statistical tools, the threshold of significance was fixed at a 5% level (i.e., P-value or probability value = 0.05).

The results were considered as follows:

- Non-significant when the probability of error was more than 5% (P-value > 0.05)
- Significant when the probability of error was less than 5% (P-value < 0.05)
- Highly significant when the probability of error was less than 0.1% (P-value < 0.001).

The smaller the P-value achieved, the more significant were the results.

3. Results

Total no of participants involved in this study was 58 among which 27 (46.6%) was males and 31 (53.4%) was females. The mean age of patients involved in study having benign and malignant liver lesions are: malignant 59.98% (32-79yr) and benign 42.72% (27-55yr).

The population enrolled in the study for final statistical analysis included 58 patients (27 males and 31 females) with their ages ranging from 27 to 79 years and a mean age of 56.71 years. The selected participants were divided into two subgroups: malignant and benign solid focal hepatic lesions.

Table 1: Cross-tabulation showing frequency distribution of different subgroups of benign and malignant liver lesions.

Malignant lesions				Benign lesions			Total cases
Meta-stases	**HCC**	**CCC**	Total	**Heman-gioma**	**FNH**	Total	
26 (44.8%)	16 (27.6%)	5 (8.6%)	47 (81.0%)	10 (17.2%)	1 (1.7%)	11 (19.0%)	**58**

The percentage distribution of 58 focal hepatic lesions was as follows:*(Table 1)*

a) 47 (81.0%) malignant solid hepatic focal lesions were subdivided as hepatocellular carcinoma (N = 16) (27.6%), metastasis (N = 26) (44.8%) {2 GIST, 3 bronchogenic carcinomas, 10 breast cancers, 3 colon cancers, 2 rectal cancers, 1 anal melanoma, 1 prostatic carcinoma, 1 carcinoma cervix and 3 ovarian carcinomas} and cholangiocarcinoma (N = 5) (8.6%).

b) 11 (19.0%) benign solid hepatic focal

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lesions were subdivided as hemangioma (N = 10) (17.2%) and focal nodular hyperplasia (N = 1) (1.7%).

Amongst the study group, forty-seven (47) patients (22 males and 25 females) had malignant hepatic focal lesions with a mean age of 59.98 years (ranging from 32 to 79 years). Eleven (11) patients (5 males and 6 females) had benign hepatic focal lesions with a mean age of 42.72 years (ranging from 27 to 55 years).

Benign liver lesions were more common in the 4th to 5th decades (~ 54.6%), whereas malignant liver lesions were more common in the 6th to 7th decades (~ 68.1%). The study group had more females with metastatic lesions than males as breast cancer was the most common primary in this group. *(Tables2-3)*

Table 2: Cross-tabulation showing mean age range distribution of benign and malignant liver lesions.

Age range (years)	**Malignant lesions (N = 47)**				**Benign lesions (N = 11)**		
	Meta-stases (26)	**HCC (16)**	**CCC (5)**	**Total (47)**	**Heman-gioma (10)**	**FNH (1)**	**Total (11)**
Up to 40	2 (4.3%)	-	-	**2 (4.3%)**	4 (36.4%)	1 (9.1%)	**5 (45.5%)**
41-50	8 (17.0%)	-	-	**8 (17.0%)**	3 (27.3%)	-	**3 (27.3%)**
51-60	6 (12.8%)	4 (8.5%)	2 (4.3%)	**12 (25.5%)**	3 (27.3%)	-	**3 (27.3%)**
61-70	9 (19.1%)	9 (19.1%)	2 (4.3%)	**20 (42.6%)**	-	-	-
Above70	1 (2.1%)	3 (6.4%)	1 (2.1%)	**5 (10.6%)**	-	-	-

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Table 3: Cross-tabulation showing gender distribution of benign and malignant liver lesions.

Gender	Malignant lesions (N = 47)				Benign lesions (N = 11)		
	Meta-stases (26)	HCC (16)	CCC (5)	Total (47)	Heman-gioma (10)	FNH (1)	Total (11)
Males	6 (12.8%)	12 (25.5%)	4 (8.5%)	**22 (46.8%)**	4 (36.4%)	1 (9.1%)	**5 (45.5%)**
Females	20 (42.6%)	4 (8.5%)	1 (2.1%)	**25 (53.2%)**	6 (54.5%)	-	**6 (54.5%)**

Methods for Final Diagnosis of Lesions

Malignant hepatic focal lesions (47):

For diagnostic confirmation, contrast-enhanced CT study (CE-CT) was performed in all patients, contrast-enhanced MRI study (CE-MRI) was performed in 16 patients and ultrasound-guided biopsy was performed in 36 patients.

In cases of HCC, provided there was liver cirrhosis or chronic HBV without cirrhosis, the guidelines of the American Association Society of Liver Disease (AASLD) were followed for the diagnosis in association with Liver Imaging Reporting and Reporting Data System version 2018 (LI-RADS v2018) on CT/MRI (in 11 HCC cases) [72]. In all other malignant lesions (in 5 cases of atypical HCC, 26 cases of metastases and 5 cases of cholangiocarcinoma), biopsy was taken.

Benign hepatic focal lesions (11):

For diagnostic confirmation, contrast-enhanced CT study (CE-CT) and contrast-enhanced MRI (CE-MRI) were performed in all patients and ultrasound-guided biopsy was performed in 1 patient.

The final diagnosis of benign solid focal hepatic lesions (hemangioma) was confirmed by assessment of three imaging modalities (US, triphasic CECT and MRI). In the case of persistent diagnostic ambiguity (in 1 case of FNH), lesion biopsy was done for histopathological confirmation. *(Table 4)*

Table 4: Cross-tabulation showing diagnostic methods among the studied groups.

Diagnostic methods	Total (N = 58)	Malignant hepatic focal lesions (N = 47)	Benign hepatic focal lesions (N = 11)
Pathology (biopsy)			
Yes	37 (63.8%)	36 (76.6%)	1 (9.1%)
No	21 (36.2%)	11 (23.4%)	10 (90.9%)

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CE-CT			
Yes	58 (100%)	47 (100%)	11 (100%)
No	0 (0%)	0 (0%)	0 (0%)
CE-MRI			
Yes	27 (46.6%)	16 (34.0%)	11 (100%)
No	31 (53.4%)	31 (66.0%)	0 (0%)

Grey-Scale Ultrasound Characteristics of Lesions

The lesions were categorized based on their grey-scale ultrasound characteristics such as median size, multiplicity, boundaries, echogenicity and vascularity. Associated features such as portal vein thrombosis and ascites were also recorded. The collected data were summarized in *Tables 5-6.*

Table 5: Cross-tabulation showing median size of benign and malignant liver lesions.

Lesion size	Total (N = 58)	Malignant hepatic focal lesions (N = 47)	Benign hepatic focal lesions (N = 11)
Median (min-max)	4.8 (2.4–11.2)	4.8 (2.4–11.2)	4.1 (2.5–9.2)

Table 6: Cross-tabulation showing multiplicity of lesions among the studied groups.

	Number and % of lesions		Total
	Solitary	**Multiple**	
Hemangioma	6	4	**10**
	60%	40%	
FNH	1	0	**1**
	100.0%	-	
Cholangiocarcinoma	5	0	**5**
	100.0%	-	
HCC	9	7	**16**
	56.3%	43.7%	

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Metastasis	1	25	**26**
	3.8%	96.2%	

Median size for malignant focal lesions was 4.8 cm (ranging from 2.4 cm to 11.2 cm) and benign focal lesions was 4.1 cm (ranging from 2.5 cm to 9.2 cm).

Hemangiomas (10):

6 (60%) were solitary, all (100%) were well-defined, 9 (90%) were hyperechoic, 2 (20%) showed increased vascularity and none were associated with portal vein thrombosis or ascites or liver cirrhosis.

Focal nodular hyperplasia (1):

The lesion was solitary, well-defined, hypoechoic, hypovascular and was not associated with portal vein thrombosis or ascites or liver cirrhosis.

Cholangiocarcinomas (5):

All (100%) were solitary, ill-defined, heteroechoic and hypovascular, 1 (20%) was associated with ascites, none were associated with portal vein thrombosis and 1 (20%) had liver cirrhosis.

Hepatocellular carcinomas (16):

9 (56.3%) were solitary, 12 (75%) were ill-defined, 10 (62.5%) were heteroechoic whereas 6 (37.5%) were hypoechoic, 12 (75%) showed increased vascularity, 7 (43.75%) had portal vein thrombosis (tumor thrombus), none were associated with ascites and 10 (62.5%) had associated liver cirrhosis.

Metastases (26):

25 (96.2%) were multiple, 21 (80.8%) were well-defined and heteroechoic (surrounded by hypoechoic halo), 5 (19.2%) showed increased vascularity, none had associated portal vein thrombosis, 7 (26.9%) were associated with ascites and 4 (15.4%) had associated liver cirrhosis.

Amongst malignant focal lesions, seven (7) cases had portal vein thrombosis, all of which were associated with HCC. None of the benign or metastatic focal lesions had associated portal vein thrombosis.

Eight (8) malignant focal lesions were associated with ascites whereas no benign focal lesion had associated ascites.

Fifteen (15) malignant focal lesions were associated with liver cirrhosis whereas no benign focal lesion had associated liver cirrhosis.

2D SWE Characteristics of Lesions

Table 7: Cross-tabulation showing SWE color characteristics of benign and malignant hepatic focal lesions and their background liver parenchyma.

Color	Total (N = 58)	Malignant focal hepatic lesions (N = 47)	Benign hepatic focal lesions (N = 11)	P-value
Focal lesions				
Yellow-green	10 (17.2%)	2 (4.3%)	8 (72.7%)	2e-16 (<0.001)
Faint blue	2	–	2	

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	(3.5%)		(18.2%)	
Mixed with red foci	46 (79.3%)	45 (95.7%)	1 (9.1%)	
Background parenchyma				
Yellow green	14 (24.1%)	14 (29.8%)	–	
Faint blue	11 (19.0%)	11 (23.4%)	–	0.00934
Dark blue	32 (55.2%)	21 (44.7%)	11 (100%)	
Mixed	1 (1.7%)	1 (2.1%)	–	

Color-coded elastograms of forty-seven (47) malignant solid hepatic focal lesions:

45 (95.7%) lesions {14 (87.5%) hepatocellular carcinomas, 26 (100%) metastases, and 5 (100%) cholangiocarcinomas} showed mixed color with red foci.

Color-coded elastograms of eleven (11) benign solid hepatic focal lesions:

8 (72.7%) lesions (typical hemangiomas) showed faint blue color, 2 (18.2%) lesions (atypical hemangiomas) showed yellow-green color and 1 (9.1%) lesion (focal nodular hyperplasia) showed mixed color with red foci.

There was a statistically significant difference of color characteristics between malignant and benign hepatic focal lesions (P-value < 0.001).

Color-coded elastograms of background liver parenchyma of forty-seven (47) malignant solid hepatic focal lesions:

21 (44.7%) lesions {5 (31.3%) hepatocellular carcinomas, 15 (57.7%) metastases, and 1 (20%) cholangiocarcinomas} showed dark blue color.

11 (23.4%) lesions {1 (6.2%) hepatocellular carcinoma, 7 (26.9%) metastases, and 3 (60%) cholangiocarcinomas} showed faint blue color.

14 (29.8%) lesions {10 (62.5%) hepatocellular carcinomas and 4 (15.4%) metastases} showed yellow-green color.

1 (2.1%) lesion {1 (20%) cholangiocarcinoma} showed mixed color.

Color-coded elastograms of background liver parenchyma of eleven (11) benign solid hepatic focal lesions:

11 (100%) lesions {10 hemangiomas and 1 focal nodular hyperplasia} showed dark blue color.

There was a statistically significant difference in color characteristics of background liver parenchyma between malignant and benign hepatic focal lesions (P-value < 0.001).

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Table 8: Cross-tabulation showing median stiffness values (kPa) of benign and malignant lesions and background liver parenchyma, and median lesion/parenchyma stiffness ratio.

Variables	Malignant hepatic focal lesions N = 47	Benign hepatic focal lesions N = 11	P-value
Focal lesions			
Median (min-max)	33.4 (20.8–51.1)	13.5 (9.8–23.7)	5.519e-16 (<0.001)
Background parenchyma			
Median (min-max)	6.4 (2.5–17.4)	4.4 (3.5–5.6)	1.448e-06 (<0.001)
Lesion/parenchyma ratio			
Median (min-max)	4.9 (1.5–17.5)	2.8 (2.1–6.8)	9.352e-05 (<0.001)

The median stiffness value of malignant solid focal lesions (33.4 kPa) was significantly higher as compared to that of benign solid focal lesions (13.5 kPa) with a P-value of <0.001.

The median stiffness value of background liver parenchyma in cases of malignant lesions (6.4 kPa) was significantly higher as compared to that of the liver parenchyma in cases of benign lesions (4.4 kPa) with a P-value of <0.001.

The median lesion/parenchyma stiffness ratio of malignant focal lesions (4.9) was significantly higher than the median lesion/parenchyma stiffness ratio of benign focal lesions (2.8) with a P-value of <0.001

.**Table 9:** Cross-tabulation showing SWE median (min-max) stiffness values (kPa) of different categories of benign and malignant lesions and background liver parenchyma, and median lesion/parenchyma stiffness ratio.

Variables	N	Median kPa stiffness value (min-max)		Lesion/ parenchyma stiffness ratio median (min-max)	P-value
		Focal lesions	Background parenchyma		
All lesions	58	31.2 (9.8–51.1)	5.75 (2.5–17.4)	3.85 (1.5–17.5)	2.2e-16 (<0.001)

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Malignant lesions	47	33.4 (20.8–51.1)	6.4 (2.5–17.4)	4.9 (1.5–17.5)	2.2e-16 (<0.001)
HCC	16	29.25 (20.8–44.2)	11.1 (3.8–16.2)	2.9 (1.5–7.6)	6.608e-10 (<0.001)
Meta-stasis	26	36.65 (25.7–48.1)	5.6 (2.5–15.4)	5.7 (2.6–17.5)	2.2e-16 (<0.001)
CCC	5	39.3 (31.3–51.1)	6.7 (3.7–17.4)	6.3 (2.9–10.4)	0.0001226 (<0.001)
Benign lesions	11	13.5 (9.8–23.7)	4.4 (3.5–5.6)	2.8 (2.1–6.8)	3.942e-06 (<0.001)
Heman-gioma	10	13.3 (9.8–15.9)	4.45 (3.5–5.6)	2.8 (2.1–3.6)	3.243e-08 (<0.001)
FNH	1	23.7	3.5	6.8	

Table 10: Cross-tabulation showing correlation between SWE median stiffness values (kPa) of different categories of benign and malignant lesions using unpaired T-test.

P-value for correlation between median stiffness values of different categories of benign and malignant lesions					
	HCC	**Metastasis**	**Hemangioma**	**FNH**	**CCC**
HCC	-	0.007263	27E-09 (<0.001)	NA	0.02795
Metastasis		-	20E-16 (<0.001)	NA	0.1733
Hemangioma			-	NA	0.001172
FNH				-	NA
CCC					-

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Table 11: Cross-tabulation showing correlation between SWE median stiffness values (kPa) of background liver parenchyma amongst different categories of benign and malignant lesions using unpaired T-test.

P-value for correlation between median stiffness values of background liver of different categories of benign and malignant lesions					
	HCC	**Metastasis**	**Hemangioma**	**FNH**	**CCC**
HCC	-	0.001461	92E-05 (<0.001)	NA	0.4439
Metastasis		-	0.0123	NA	0.4565
Hemangioma			-	NA	0.1974
FNH				-	NA
CCC					-

Table 12: Cross-tabulation showing correlation between median lesion/parenchyma stiffness ratio of different categories of benign and malignant lesions using unpaired T-test.

P-value for correlation between lesion/parenchyma ratio of different categories of benign and malignant lesions					
	HCC	**Metastasis**	**Hemangioma**	**FNH**	**CCC**
HCC	-	0.000138	0.7902	NA	0.08224
Metastasis		-	33E-05 (<0.001)	NA	0.6308
Hemangioma			-	NA	0.05592
FNH				-	NA
CCC					-

Median stiffness values (kPa) in different categories of malignant solid hepatic focal lesions (N = 47):

Cholangiocarcinoma was the stiffest lesion (median stiffness value = 39.3 kPa) followed by metastases (median stiffness value = 39.3 kPa) and HCC (median stiffness value = 29.25 kPa).

There was statistically significant difference between median stiffness values of Cholangiocarcinoma and HCC (P-value = 0.028), Cholangiocarcinoma and Metastases (P-value = 0.173), and Metastases and HCC (P-value = 0.007).

Median stiffness values (kPa) in different categories of benign solid hepatic focal lesions (N = 11):

FNH had much higher stiffness value (23.7 kPa) than hemangioma (median stiffness value = 13.3 kPa). (However, test for statistical significance could not be applied as a single value could not be compared with a set of values.)

Comparison of median stiffness values (kPa) in different categories of malignant and benign solid hepatic focal lesions (N = 58):

There was statistically significant difference between median stiffness values of Hemangioma

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and Cholangiocarcinoma (P-value = 0.001), Hemangioma and HCC (P-value < 0.001), and Hemangioma and Metastases (P-value < 0.001).

The stiffness value of FNH was close to the median stiffness value of HCC and lower than the median stiffness values of Metastases and Cholangiocarcinoma. (However, test for statistical significance could not be applied as a single value could not be compared with a set of values.)

Median stiffness values (kPa) of background liver parenchyma in different categories of malignant solid hepatic focal lesions (47):

The highest liver parenchyma stiffness was associated with cases of HCC (due to associated liver cirrhosis) (median stiffness value = 11.1 kPa), followed by Cholangiocarcinoma (median stiffness value = 6.7 kPa), and Metastases (median stiffness value = 5.6 kPa)

There was a statistically significant difference between median background liver parenchyma stiffness values of HCC and Metastases (P-value = 0.001). However, the statistical difference was not high when the median background liver stiffness value of HCC was compared with Cholangiocarcinoma (P-value = 0.444) or Metastases was compared with Cholangiocarcinoma (P-value = 0.457).

Median stiffness values (kPa) of background liver parenchyma in different categories of benign solid hepatic focal lesions (11):

The stiffness value of liver parenchyma in the case of FNH (3.5 kPa) was close to cases of Hemangioma (median stiffness value = 4.45 kPa). (However, test for statistical significance could not be applied as a single value could not be compared with a set of values.)

Comparison of median stiffness values (kPa) of background liver parenchyma in different categories of malignant and benign solid hepatic focal lesions (N = 58):

The statistically significant difference in median stiffness values of background liver was highest between HCC and benign lesions (P-value < 0.001), followed by Metastases and benign lesions (P-value = 0.01), and Cholangiocarcinoma and benign lesions (P-value = 0.197).

Comparison of median lesion/parenchyma stiffness ratio in different categories of malignant and benign solid hepatic focal lesions (N = 58):

The median lesion/parenchyma stiffness ratio value was lower in HCC (2.9) as compared to other malignant lesions (Metastases = 5.7 and Cholangiocarcinoma = 6.3 with P-values of <0.001 and 0.08 respectively) whereas it was similar to that of benign lesions (2.8) with no statistically significant difference (P-value = 0.79).

There was no statistically significant difference between the median lesion/parenchyma stiffness ratio of Metastases and Cholangiocarcinoma (P-value = 0.63).

FNH showed a higher stiffness ratio (6.8) as compared to HCC (2.9) and Hemangioma (2.8) which was similar to Cholangiocarcinoma and Metastases (6.3 and 5.7 respectively).

Table 13: Cross-tabulation showing various parameters to evaluate the diagnostic accuracy of SWE stiffness threshold cut-off value (kPa) for differentiation of benign from malignant lesions based on ROC analysis.

Measure	Value	Derivations
Sensitivity	1.0000	TPR = TP / (TP + FN)
Specificity	0.9091	SPC = TN / (FP + TN)
Precision/	0.9792	PPV = TP / (TP + FP)

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Positive Predictive Value		
Negative Predictive Value	1.0000	NPV = TN / (TN + FN)
False Positive Rate	0.0909	FPR = FP / (FP + TN)
False Discovery Rate	0.0206	FDR = FP / (FP + TP)
False Negative Rate	0.0000	FNR = FN / (FN + TP)
Accuracy	0.9828	ACC = (TP + TN) / (P + N)
F1 Score	0.9895	F1 = 2TP / (2TP + FP + FN)
AUC (area under the curve)	0.9545	

The receiver operating characteristic (ROC) curve analysis was applied to evaluate the diagnostic accuracy of SWE median stiffness values for differentiation of benign from malignant solid hepatic focal lesions using a threshold cutoff value of *15.9 kPa* with the area under the curve (AUC) = 0.9545.

All malignant lesions (47) (100%) had a value > 15.9 kPa and 10 out 11 benign lesions (90.9%) had a value < 15.9 kPa.

The ROC analysis resulted in 100% sensitivity, 90.91% specificity, 97.92% positive predictive value (PPV), 100% negative predictive value (NPV) and 98.28% accuracy. *(Table 13)*

4. Discussion

In this study, benign solid focal lesions were 4.1 cm and malignant were 4.8 cm. There was no association between lesion size, benign or malignant status, and stiffness (kPa) (P=0.6968). Abdel-Latif et al. [22],Guibal et al. [23], and Choong et al. [24] observed no statistical connection between lesion size and stiffness.

In color-coded elastograms, 45 malignant lesions (95.7%) had red foci, but just one benign lesion, FNH (9.1%), did. Thus, normal and malignant solid focal lesions have statistically different SWE colours (P=0.001). Abdel-Latif et al.[22], Guibal et al.[23], and Park et al.[25] all supported this interpretation.

In the current investigation, benign lesions (13.5 kPa) were substantially less stiff than malignant lesions (33.4 kPa) (P=0.001). This observation was consistent with studies by Abdel-Latif et al. [22] (median stiffness value for benign lesions = 10.68 kPa and for malignant lesions = 20.22 kPa, P-value 0.001), Guibal et al. [23] (mean stiffness value for benign lesions = 18.53 13.5 kPa and for malignant lesions = 26.9 18.8 kPa, P-value =<0.0001,Park et al. [25](mean stiffness value for malignant lesions = 60.41 ± 47.81 kPa and for benign lesions = 22.05 ± 17.24 kPa, P-value = 0.0001), and Gerber et al. [26] (median stiffness value for malignant lesions = 36 kPa and for benign lesions = 16.4 kPa, P-value <0.0001)

FNH had a median stiffness value of 23.7 kPa, which was greater than that of hemangiomas (13.3 kPa) among benign solid focal lesions. These results were in line with the findings of Abdel-Latif et al. [22] (median stiffness value of FNH = 26.7 kPa and hemangioma = 10.5 kPa), Guibal et al.[23] (mean stiffness value of FNH = 33 ± 14 kPa and hemangioma = 13.8 ± 5.5 kPa), and Park et al. [25] (mean stiffness value of FNH = 27.02 ± 4.14 and hemangioma = 12.91 ± 9.42 kPa), but Gerber et al. [26] found no statistically significant difference in elasticity values across various benign FLLs [median stiffness values of FNH = 16.55 (2.1–69.7) kPa and hemangioma = 16.35 (5.4–71.9) kPa]. Yu and Wilson supported their findings by asserting that the stiffness elevations corresponded to the

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fibrous component, making FNH the stiffest benign lesion owing to the central scar formation.

The median stiffness value of the hemangioma was 13.3 kPa, and that of the background hepatic parenchyma for the same cases was 4.45 kPa, with a statistically significant difference (P-value 0.001). These findings were in accordance with the studies of Abdel-Latif et al. [22] (median stiffness value of hemangioma = 10.5 kPa and background parenchyma = 5.84 kPa), Gerber et al. [26] (median stiffness value of hemangioma = 16.35 kPa and background parenchyma = 8.5 kPa), Park et al. [25] (mean stiffness value of hemangioma = 12.91 9.42 kPa and background parenchyma = 5.5 2.8 kPa), Guibal et al. [23], and Qiang et al. [28], who concluded that the stiffness of the hepati Kim et al. (61) supported these observations by stating that hemangiomas are histologically composed of vast blood-filled endothelial-lined spaces separated by fibrous septations and vascular thrombi, which are accountable for their higher stiffness values than the normal liver.

SWE mean stiffness values for focal fatty sparing are 15.15 ± 11.38 kPa, hematomas are 31.05± 1.34 kPa, and fibrosis is 6.5 kPa, according to Park et al. [25]. Gerber et al. (1996**)** enclosed one case of adenoma with a median stiffness of 8.9 kPa. According to Guibal et al. [23], the mean SWE values for focal fatty sparing were 6.6 0.3 kPa, 53.7 4.7 kPa for focal scars, and 9.4 4.3 kPa for adenomas.Guibal et al. (1996) elucidated that the stiffness values of an adenoma were higher than those of the surrounding parenchyma because adenomas are made up of large hepatocytes supported by a weak collagen framework and lack biliary canaliculi. Unfortunately, no cases from these categories were included in the current study.

In the current study, the stiffest lesion amongst all types of benign and malignant solid FLLs was cholangiocarcinoma (median stiffness value = 39.3 kPa), whose stiffness values were higher than those of other malignant focal lesions. Thus, it was noted that even though FNH also contains a fibrotic component and shows high stiffness values, it could not match the stiffness of cholangiocarcinoma. The same was also concluded by Abdel-Latif et al. [22] (median stiffness value of FNH = 26.7 kPa and cholangiocarcinoma = 35.9 kPa), Guibal et al. [23] (mean stiffness value of FNH = 33 ± 14.7 kPa and cholangiocarcinoma = 56.9 ±25.6 kPa), and Gerber et al. [26].

Sirica et al. [29] and Okamoto et al. [30] explained these results by stating that cholangiocarcinomas contain a major fibrotic component, which is also a significant element of their malignant progression. Heide et al. [(31)] added that this fibrotic component is likely to be the cause of the increased stiffness seen in cholangiocarcinoma.

The median stiffness value of hepatocellular carcinoma (HCC) (29.25 kPa) was lower than that of metastasis (36.65 kPa) and cholangiocarcinoma (39.3 kPa) and was higher than that of hemangiomas (13.3 kPa). The minimum stiffness value of HCC was 20.8 kPa, which was lower than FNH (23.7 kPa); however, in our study, 12 out of 16 cases (75% of the total) showed higher stiffness values than FNH.

The studies of Abdel-Latif et al. [22], Guibal et al. [23], Kim et al. [32], and Frulio et al. [33] suggested that hepatocellular carcinoma was harder than all benign focal lesions but softer than benign focal lesions that showed fibrotic components such as focal nodular hyperplasia. Abdel-Latif et al. [22] reported that HCC (median stiffness value = 17.6 kPa) had lower stiffness than that of metastasis (median stiffness value = 25.5 kPa) and cholangiocarcinoma (median stiffness value = 35.9 kPa) and higher stiffness than the median stiffness values of all benign hepatic lesions (10.68 kPa) except FNH (median stiffness value = 26.7 kPa). Guibal et al. (2001) reported that the SWE mean stiffness value (in kPa) for HCCs was 14.86 ±10, for metastasis it was 28.8 ± 16, and for cholangiocarcinomas it was 56.9 ±25.6 kPa, with a statistically significant difference in tissue elasticity between cholangiocarcinoma and HCC (P-value = 0.0004). Choong et al. [24], in contrast to our findings, stated that the SWE values of HCC (51.45 ± 14.96 kPa) showed no statistically significant difference from those of metastasis (49.89 ± 13.82 kPa).

In the current study, the median stiffness of all solid FLLs was 31.2 kPa, which was significantly

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higher than the surrounding liver parenchyma (5.75 kPa), with a P-value of 0.001. For the malignant group of lesions, the median lesion stiffness value was 33.4 kPa, which was significantly higher than the median background parenchyma stiffness (6.4 kPa) (P-value 0.001). For the benign group of lesions, the median lesion stiffness value was 13.5 kPa, which was significantly higher than the median background parenchyma stiffness (4.4 kPa) (P-value 0.001). When the median stiffness values of various subgroups of FLLs were compared to the median stiffness values of their background liver parenchyma, the same results were obtained. Also, the highest median stiffness of background liver was seen in cases of HCC (11.1 kPa) in our study, which was significantly higher when compared with the background liver stiffness of other subgroups of FLLs. It was also noted that the minimum stiffness value of HCC (20.8 kPa) was close to the maximum stiffness value of background liver parenchyma that was seen in cases of HCC (16.2 kPa).

According to Gerber et al. [26], the median stiffness of all FLLs (28.6 kPa) was significantly higher than the surrounding liver (9.9 kPa) (P-value 0.0001), and the surrounding liver in patients with HCC had the highest stiffness (P-value 0.001) in comparison to the surrounding liver of other subgroups. According to Abdel-Latif et al. [22], the median stiffness value of all FLLs (18.37 kPa) was significantly higher than that of the surrounding liver parenchyma (6.47 kPa) (P-value 0.001), and the surrounding liver in patients with HCC had the highest median stiffness value of 13.2 kPa (P-value 0.001) when compared to the surrounding liver parenchyma of other subgroups.

Abdel-Latif et al. [28] included 21 cases of HCC, two of which had stiffness values (15.27 and 15.1 kPa) that were lower than the surrounding liver parenchyma (18.2 and 17.8, respectively); however, 19 cases had stiffness values that were greater than the liver parenchyma.Likewise, Guibal et al. [23] included 25 cases of HCC, out of which 6 cases showed lower stiffness values and 19 cases showed higher stiffness values than the surrounding liver parenchyma.

This was addressed by Guibal et al. [32] and Gallotti et al. [34] by stating that HCCs in cirrhotic livers may have relatively softer values when compared to the rigid surrounding parenchyma.

The current study showed a statistically significant difference between the median stiffness values of HCC (29.25 kPa) and cholangiocarcinoma (39.3 kPa), with cholangiocarcinoma showing higher stiffness (P-value = 0.028). Similar conclusions were drawn by the studies of Abdel-Latif et al. [22] (median stiffness value of cholangiocarcinoma = 35.9 kPa and HCC = 17.6 kPa), Gerber et al. [26] (median stiffness value of cholangiocarcinoma = 70.7 kPa and HCC = 44.8 kPa), and Guibal et al. [23] (P-value = 0.0004). It was mentioned by Guibal et al. [23] and Gerber et al. [26] that in certain cases, cholangiocarcinomas and hepatocellular carcinomas might have similar imaging features on CT and MRI, making differentiation between the two difficult. Hence, these significant differences in SWE characteristics may help solve the problem.

In this study, the SWE values of metastases varied widely depending on the primary tumour type; for instance, metastases from GIT cancers (8 cases) had lower stiffness (median value = 20.7 kPa) than metastases from breast cancer (10 cases) (median value = 40.2 kPa). Similar findings were reported by Abdel-Latif et al. [22,] who found that the stiffness of colorectal metastases (6 cases) (median value = 22.54 kPa) was lower than that of breast cancer metastases (7 cases) (median value = 26.25 kPa), and Guibal et al. [23,] who found that the stiffness of carcinoid tumour metastases (mean value = 30.7 kPa) was higher than that of metastases from gastro-intestinal tract adenocarcinomas (median value = 21.8 kPa).

When the median lesion/parenchyma stiffness ratio was evaluated, it was observed in our study that overall, the value was higher for malignant lesions. However, when various subgroups were compared, it was observed that the ratio was lower in HCC (2.9) as compared to other malignant lesions (metastases = 5.7 and cholangiocarcinoma = 6.3), whereas it was similar to that of benign lesions (2.8).

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There was no statistically significant difference between the median lesion/parenchyma stiffness ratio of metastases and cholangiocarcinoma. Also, FNH showed a higher stiffness ratio (6.8) as compared to HCC (2.9) and hemangiomas (2.8), which were close to cholangiocarcinoma and metastases (6.3 and 5.7, respectively). These observations could be attributed to fibrosis in the surrounding liver parenchyma, which is associated with HCC.

These results were concordant with the studies of Abdel-Latif et al. [22], who stated that the lesion/parenchyma stiffness ratio for HCC (1.37) was lower than that of cholangiocarcinoma (4.6) and metastasis (4.2); Park et al. [25]; and Wall et al. [38], who described that HCC showed a lower ratio than all other malignant FLLs and showed a similar value when compared with benign FLLs.

The main role of the SWE technique, according to the studies of Guibal et al. [23], Gerber et al. [26], Park et al. [25], Brunel et al. [35], Ferraioli et al. [36], and Xie et al. [37], was to establish differences between adenoma and FNH in the benign category and between HCC and cholangiocarcinoma in the malignant category, as some of these cases may have diagnostic overlap and conflict when standard radiological imaging modalities alone are used. In agreement with this interpretation, the current study showed that the median stiffness value of cholangiocarcinoma (39.3 kPa) was significantly higher than that of hepatocellular carcinoma (29.25 kPa), with a P-value of 0.028. Unfortunately, cases of hepatic adenoma were not included in this study, and thus, a distinction between adenoma and FNH could not be established. However, citing prior studies, Guibal et al. [23] included 10 cases of adenoma with a mean stiffness value of 9.4 ±4.3 kPa and 16 cases of FNH with a mean stiffness value of 33 ± 14.7 kPa, and Brunel et al. [35] included 19 cases of adenoma with a mean stiffness value of 12.08 ± 10.68 kPa and 57 cases of FNH with a mean stiffness value of 46.99 ± 31.15 kPa.

When receiver operating characteristic (ROC) curve analysis was applied to evaluate the diagnostic accuracy of SWE median stiffness values for differentiation of benign from malignant solid hepatic focal lesions using a threshold cut-off value of *15.9 kPa* with the area under the curve (AUC) = 0.9545, this study resulted in 100% sensitivity, 90.91% specificity, 97.92% positive predictive value (PPV), 100% negative predictive value (NPV), and 98.28% accuracy.

These results were concordant with the study of Abdel-Latif et al. [22], where, in a sample size of 75 cases, using a threshold cut-off value of 14.165 kPa with an AUC of 0.834, the ROC curve yielded 98.1% sensitivity, 78.3% specificity, and 92% accuracy. However, in the study of Park et al. [25], using a threshold cut-off value of 30.8 kPa with an AUC of 0.79 in a sample size of 136 cases, the ROC curve yielded 70.6% sensitivity and 82.4% specificity. The difference in sensitivity could be due to a difference in sample size.

5. Conclusion

This study has demonstrated that 2D shear wave sono-elastography is a robust technique and is capable of evaluating stiffness changes in the liver associated with solid focal liver lesions, which helps in distinguishing benign from malignant lesions and also in their sub-categorization, i.e., differentiating focal nodular hyperplasia from hemangioma and differentiating hepatocellular carcinoma from cholangiocarcinoma and metastases, with high sensitivity and accuracy. Thus, it can be added to routine grey-scale sonographic examinations for rapid, cost-effective, non-invasive, and non-contrast assessments to aid the diagnosis and further management.

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