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Role of Ultrasound Shear-Wave Elastography in Differentiating Hepatocellular Carcinoma from Other Solid Hepatic Focal Lesions in Correlation with Triphasic CT Findings

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ABSTRACT

Background: Improved screening and diagnostic tools have improved early detection of hepatocellular carcinoma (HCC), a leading cause of cancer-related death in Egypt, especially among high-risk patients with chronic viral hepatitis**.**

Aim: This study aimed to evaluate the diagnostic accuracy of stiffness values between hepatocellular carcinoma (HCC) and other solid hepatic focal lesions, as measured by shear wave elastography (SWE), and to correlate the results with triphasic computed tomography (CT) studies. **Patients and methods:** Thirty-four patients with localized liver lesions participated in this prospective observational study. Patients were collected from Cairo University's Faculty of Medicine's Clinical Oncology, Surgery, and Endemic Medicine Departments.

Results: SWE stiffness values showed no significant difference among benign lesions, but a significant difference among malignant ones, with HCC and metastases showing lower stiffness than cholangiocarcinoma ($P < 0.001$). SWE differentiated HCC from cholangiocarcinoma and focal fatty lesions ($P < 0.001$, 0.017), but not from metastases or hemangiomas. A significant association was found between lesion type and number, ascites, and splenomegaly. Only hemangiomas showed a significant correlation between stiffness and size ($r = 0.848$, $P = 0.033$). At a cutoff >18.6 kPa, SWE achieved 95.2% sensitivity and 84.6% specificity in distinguishing malignant from benign lesions (AUC = 0.886, $P < 0.001$).

Conclusion: SWE differentiated HCC from cholangiocarcinoma and focal fatty lesions but not from other lesions. It may help distinguish cholangiocarcinoma from HCC.

Keywords: Shear wave elastography, Hepatocellular carcinoma, Focal liver lesions, Triphasic CT.

INTRODUCTION

With an increasing global occurrence, hepatocellular carcinoma (HCC) is currently regarded as the second leading cause of cancer-related mortality. HCC ranks sixth among cancers in women and second among cancers in men in Egypt. HCC is considered the main complication of cirrhosis, and shows a growing incidence in Egypt, which may be the result of the shift in the relative importance of hepatitis C virus (HCV) and hepatitis B virus (HBV) as the main risk factors and also the improvement in the screening programs and the diagnostic modalities, Patients with chronic infection with HBV or HCV are at higher risk for developing HCC, and should be enrolled in surveillance programs using ultrasound and serum α-fetoprotein [1, 2]**.** Patients with focal lesions in ultrasound require further evaluation with triphasic computed tomography (CT), and either MRI, liver biopsy or both to confirm HCC diagnosis [2].

Shear wave elastography (SWE) is a technology that uses ultrasound shear waves to provide a noninvasive, reproducible, and easily performed way of measuring liver stiffness [3]**.** It provides a local evaluation of an organ's point of interest in kilopascals (kPa). The major advantages of SWE are the reproducibility, operator independency, higher spatial resolution, and the ability to establish a quantitative evaluation of stiffness values without manual compression artifacts. SWE has been demonstrated to be helpful in assessment of liver fibrosis degree [4], and may be used as an adjunct to conventional ultrasound in differentiation and characterization of hepatic focal lesions [5]**.**

SWE appears to be useful in the following situations, based on the initial findings of the research of focal liver lesions: For the diagnosis of HCC in addition to hepatic cirrhosis, distinguishing between localized nodular hyperplasia and adenomas, identifying liver metastases and differentiation between benign and malignant hepatic focal lesions [6-8].

Numerous studies have been published, which proved the real-time elastography efficiency in differentiating the stiffness of the prostate, breast, thyroid, or pancreatic tumors [9]**.** A small number of studies have investigated the stiffness of focal liver lesions quantitatively [5]**.** Therefore, this study aimed to evaluate the diagnostic accuracy of stiffness value between HCC and other solid hepatic focal lesions, as measured by SWE and to correlate the results with triphasic CT studies.

PATIENTS AND METHODS

Thirty-four patients with localized liver lesions participated in this prospective observational study. Patients were collected from Cairo University's Faculty of Medicine's Clinical Oncology, Surgery, and Endemic Medicine Departments.

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Inclusion criteria: Male or female patients with at least one hepatic focal lesion larger than 1 cm in diameter that was clearly seen on a standard US scan were at least 18 years old.

Exclusion criteria: Patients with focal lesions smaller than 1 cm, those with previously treated focal lesions by interventional radiology, patients unable to hold their breath as required, and those who refused to participate in the study.

Methods: Every patient underwent a thorough clinical evaluation, which included age, sex, and clinical appearance. Medical history was taken including diabetes and smoking status. Laboratory investigations included HCV Ab, HBsAg, and HBc totalAb. Abdominal ultrasonography was performed using gray scale abdominopelvic ultrasound and SWE [Toshiba Aplio 500 ultrasound system and a curved array transducer (6C1)] to acquire baseline B-mode images for assessment of hepatic focal lesions regarding number, site, size, margin, and echogenicity, liver size, liver parenchymal pattern, portal vein thrombosis, and presence of ascites. SWE acquisitions of each hepatic focal lesion were performed during breath holding without deep inspiration. For each SWE image, a region of interest (ROI) was placed within the lesion to quantitatively evaluate stiffness, avoiding large liver vessels. From 3 to 8 measurements were taken per lesion, and the machine estimated the velocity of the propagated shear wave in the ROI and automatically translated it to stiffness in kilopascals (KPs). In cases of multiple lesions, measurements were taken from the most accessible lesion. When multiple successful measurements were obtained, the results were presented as the mean value of all measurements. The data obtained by SWE was compared to triphasic CT findings. Triphasic CT scanning was performed for patients with detected focal hepatic lesions using Semense Emotion MSCT 16 channels and Toshiba Aquilion MSCT 64 channels at 120 kVp and 200–250 mAs. Patients received IV contrast at 1.5 ml/kg (total dose 80–100 ml) following departmental protocol. The liver was scanned in arterial (20–40 seconds), portal (60–90 seconds), and stages that are delayed by 2 to 5 minutes. The enhancement pattern of each lesion was assessed in terms of mixed pattern, iso-density to liver parenchyma, hyper-enhancement, or hypo-enhancement. The radiological diagnosis of early HCC, the hallmark of HCC diagnosis, was made using a special dynamic radiological behavior (arterial phase contrast uptake with venous/late phase washout) [(10)].

Ethical approval:

This study was approved by ethical committee of Faculty of Medicine, Cairo University. An informed consent was obtained from all participants. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

SPSS version 28 was used for the statistical analysis (IBM Co., Armonk, NY, USA). ANOVA (F) test with post hoc test (Tukey) was used to evaluate quantitative parametric data, which were displayed as mean and standard deviation (SD). The Mann Whitney test was used to evaluate quantitative non-parametric data, which were displayed as the median and interquartile range (IQR). The Chi-square test was used to examine the qualitative variables, which were displayed as frequency and percentage (%). The degree of correlation between two quantitative variables was evaluated using Pearson's Correlation coefficient (r). The diagnostic performance of stiffness values determined by SWE was evaluated using a ROC curve with area under the curve (AUC), an area under the curve of > 50% indicates acceptable performance, while an area of almost 100% indicates the best performance for the test. P values with two tails ≤ 0.05 were deemed statistically significant.

RESULTS

Table (1) showed that this cross-sectional study included 34 patients (23 males & 11 females) with hepatic focal lesions > 1 cm, aged 22–68 years (mean 49.68 ± 9.73). Diabetes was present in 29.4%, smoking in 32.4%, and HCV in 35.4%. Of all patients, 13 had benign lesions (hemangiomas, focal fatty changes, adenoma & hemangiopericytoma) and 21 had malignant lesions (HCC, metastases & cholangiocarcinoma).

Table (1): Baseline characteristics and final diagnoses of the Studied patients (n=34)

		Total patients (n=34)
Age (years)	**Mean ± SD**	49.68 ± 9.73
	Range	22 – 68
Sex	**Male**	23 (67.6%)
	Female	11 (32.4%)
Risk factors	**DM**	10 (29.4%)
	Smoking	11 (32.4%)
	HCV	12 (35.3%)
	N	**%**
Benign	13	38.2
Hemangioma	6	17.6
Focal fatty sparing	3	8.8
Focal Fatty infiltration	2	5.9
Adenoma	1	2.9
Hemangiopericytoma	1	2.9
Malignant	21	61.8
HCC	11	32.4
Metastases	8	23.5
Cholangiocarcinoma	2	5.9

Table (2) showed that when comparing the stiffness of benign and malignant lesions using SWE, there was a statistically significant difference (P<0.001) because the malignant lesions were more rigid than the benign ones.

Table (2): Relation between focal lesions and SWE stiffness values of the studied patients

	Benign (n=13)	Malignant (n=21)	P value
SWE mean value of stiffness (KPa)	12.6 (10.15-41.52)	30.9 (25.58-58.48)	**<0.001***
SWE median value of stiffness (KPa)	12.9 (10.45-38.44)	34.6 (24.85-54.46)	**<0.001***

Data are presented as median (IQR), *: Statistical significance as P value < 0.05.

Table (3) showed that there was no statistically significant difference in SWE stiffness values among benign focal lesions, whereas a statistically significant difference was observed among malignant lesions, with HCC and metastases demonstrating significantly lower stiffness than cholangiocarcinomas (P < 0.001), while HCC and metastatic lesions showed comparable stiffness values.

Table (3): Comparison of SWE stiffness values among different benign and malignant hepatic focal lesions

Lesion Type	Category	Number of Cases (n)	SWE Mean Stiffness (kPa)	SWE Median Stiffness (kPa)	P Value
Focal Fatty Sparing	**Benign**	**3**	**9.77 ± 0.71**	**10.2 ± 0.44**	**0.113**
Focal Fatty Infiltration	**Benign**	**2**	**16.18 ± 6.88**	**16.42 ± 7.00**	**0.113**
Hemangioma	**Benign**	**6**	**11.4 ± 1.27**	**11.75 ± 0.49**	**0.113**
Adenoma & Hemangiopericytoma	**Benign**	**2**	**32.9 ± 24.18**	**30.65 ± 19.16**	**0.113**
Hepatocellular Carcinoma (HCC)	**Malignant**	**11**	**30.28 ± 8.20**	**30.02 ± 9.47**	**<0.001***
Metastases	**Malignant**	**8**	**31.12 ± 8.68**	**31.48 ± 9.95**	**<0.001***
Cholangiocarcinoma	**Malignant**	**2**	**84.2 ± 31.96**	**73.05 ± 23.26**	**<0.001***

Table (4) showed a significant association between lesion type and number, ascites, and splenomegaly (P = 0.028, 0.013, 0.006). Metastases were more often multiple and associated with ascites, while splenomegaly was more common in HCC. SWE differentiated HCC from cholangiocarcinoma and focal fatty lesions (P < 0.001 and 0.017 respectively), but not from metastases & hemangioma, or adenoma. Cholangiocarcinoma showed the highest stiffness, and focal fatty lesions had lower stiffness than metastases (P = 0.019).

Table (4): Comparison of Hepatic Lesions by US Features and SWE Stiffness

	HCC (n=11)	Metastases (n=8)	Cholangio-Carcinoma (n=2)	Focal fatty lesions (n=5)	Hemangioma (n=6)	Adenoma & Hemangiope-ricytoma (n=2)	P value
Focal lesions number							
Single	7 (63.6%)	2 (25%)	1 (50%)	5 (100%)	5 (83.3%)	2 (100%)	**0.028***
Multiple	4 (36.4%)	6 (75%)	1 (50%)	0 (0%)	1 (16.7%)	0 (0%)	
Focal lesions size (cm)							
Mean ± SD	4.02±1.27	3.78 ± 2.45	5.55 ± 0.07	2.26 ± 0.76	2.55 ± 1.82	4.6 ± 4.1	0.184
Range	2.7 – 6.4	1.5 – 8.5	5.5 – 5.6	1 - 3	1 - 6	1.7 – 7.5	
Focal lesions location							
Right	7 (63.6%)	2 (25%)	2 (100%)	5 (100%)	3 (50%)	2 (100%)	
Left	3 (27.3%)	1 (12.5%)	0 (0%)	0 (0%)	2 (33.3%)	0 (0%)	0.06
Bilobar	1 (9.1%)	5 (62.5%)	0 (0%)	0 (0%)	1 (16.7%)	0 (0%)	
Focal lesions boundaries							
Well defined	6 (54.5%)	5 (62.5%)	1 (50%)	5 (100%)	6 (100%)	1 (50%)	0.078
Ill-defined	5 (45.5%)	3 (37.5%)	1 (50%)	0 (0%)	0 (0%)	1 (50%)	
Focal lesions echogenicity							
Isoechoic	1 (9.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Hyperechoic	7 (63.6%)	4 (50%)	0 (0%)	2 (40%)	3 (50%)	1 (50%)	0.157
Hypoechoic	3 (27.3%)	3 (37.5%)	0 (0%)	3 (60%)	3 (50%)	0 (0%)	
Heterogeneous	0 (0%)	1 (12.5%)	2 (100%)	0 (0%)	0 (0%)	1 (50%)	
Findings							
Ascites	1 (9.1%)	5 (62.5%)	1 (50%)	0 (0%)	0 (0%)	0 (0%)	**0.013***
Splenomegaly	7 (63.6%)	3 (37.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	**0.006***
Portal vein thrombosis	0 (0%)	0 (0%)	1 (50%)	0 (0%)	0 (0%)	0 (0%)	0.283
Liver size							
Normal	5 (45.5%)	6 (75%)	1 (50%)	2 (40%)	2 (33.3%)	1 (50%)	
Shrunken	4 (36.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0.174
Enlarged	2 (18.2%)	2 (25%)	1 (50%)	3 (60%)	4 (66.7%)	1 (50%)	
Mean SWE							
Mean ± SD	30.28 ±8.2	31.12 ±8.68	84.2 ±31.96	10.42 ±1.21	16.18 ±6.88	32.9 ±24.18	**<0.001***
Range	21.2-46	13.3-39.8	61.6-106.8	9-12.3	9.4-28.8	15.8-50	

Data are presented as mean ± SD or frequency (%), *: Statistical significance as P value<0.05.

Table (5) showed that no correlation was detected between the stiffness and the size of HCC, metastasis and focal fatty lesions, while there was a statistically significant correlation between the mean stiffness value of hemangioma measured by SWE and their size (r=0.848, P=0.033).

Table (5): Correlation between the stiffness of different hepatic lesions by SWE and their size

	r	P value
HCC	0.13	0.704
Metastases	0.319	0.442
Cholangiocarcinoma	---	---
Focal fatty	-0.149	0.811
Hemangioma	0.848	**0.033***
Adenoma and Hemangiopericytoma	---	---

r: Pearson correlation coefficient, ---: Indicates not enough data to estimate the correlation coefficient.

Table (6) showed that at cut off point >18.6 KPs, the mean stiffness value measured by SWE was able to differentiate between benign and malignant lesions (AUC=0.886, P<0.001) with sensitivity of 95.24%, specificity of 84.62%, PPV of 90.9% and NPV of 91.7%.

Table 6: The diagnostic performance of mean stiffness value by SWE regarding malignancy

	Cut off	AUC	Sensitivity	Specificity	PPV	NPV	P value
SWE stiffness value of lesion (KPs	>18.6	0.886	95.24%	84.62%	90.9%	91.7%	**<0.001***

*: Statistical significance as P value<0.05, AUC: Area under the curve, PPV: Positive predictive value, NPV: Negative predictive value.

CASE PRESENTATION

Case (1): 55 years old male patient presented with abdominal pain.

Imaging Findings:

Grey scale B-mode Ultrasonography (A):

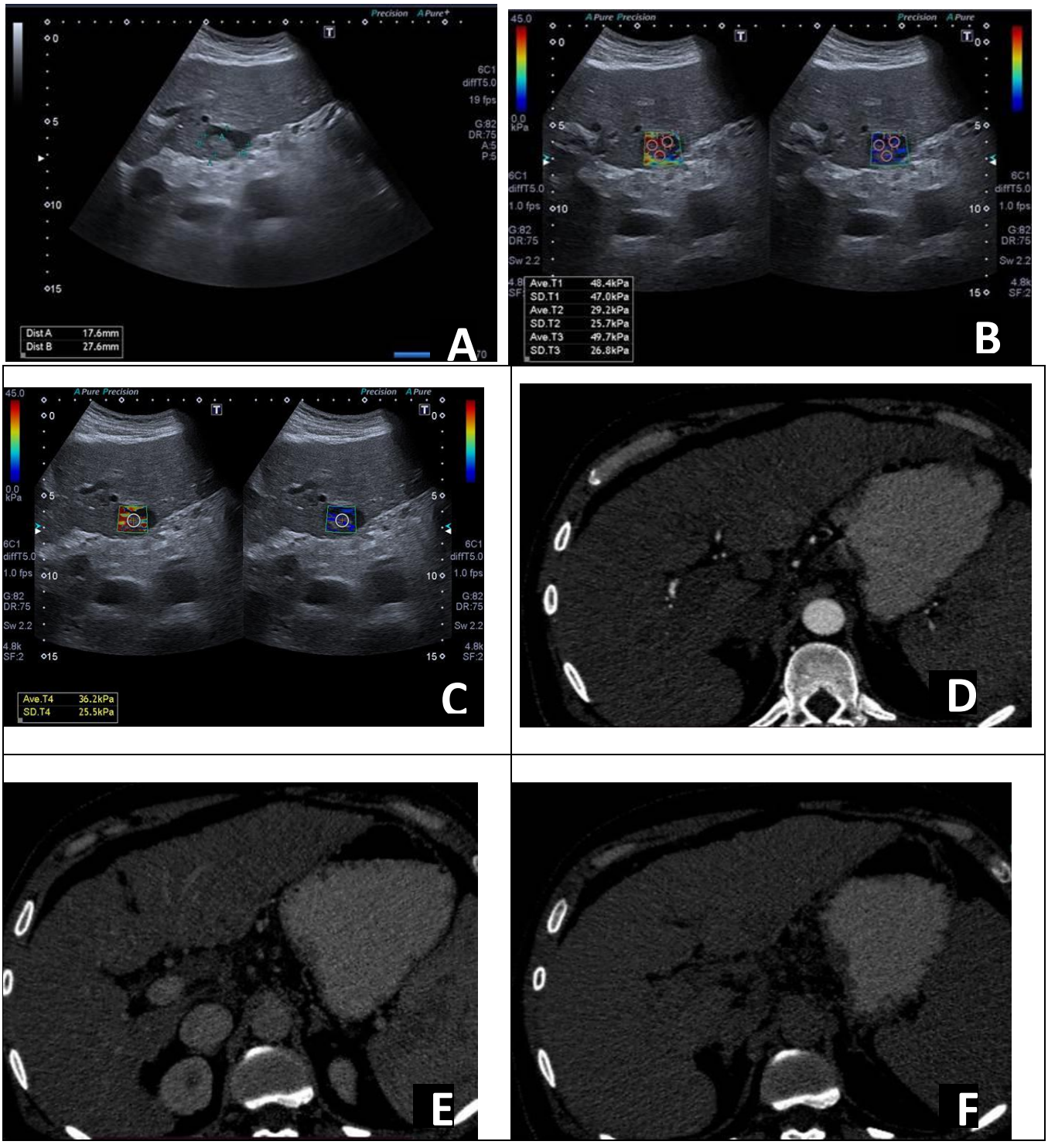
Cirrhotic liver changes showing focal lesion in segment IVb, measuring about 2.7 X 1.7 cm.

Shear wave sono-elastography stiffness values of the focal lesion (B, C): Maximum stiffness = 49.7kPa, Minimum stiffness = 29.2kPa and Calculated average stiffness = 39.9kPa.

Axial contrast enhanced triphasic CT study, arterial (D), portal (E) & delayed (F) phases:

Advanced cirrhotic liver changes with segment IVb focal lesion showing arterial enhancement with rapid washout of the contrast in the sequential phases with retained capsular enhancement.

Diagnosis: Hepatocellular carcinoma.



Case (2): 54 years old male patient presented with abdominal pain.

Imaging findings:

Grey scale B-mode Ultrasonography (A): Normal sized cirrhotic liver showing 3 well defined hypoechoic focal lesions seen in segment VI, the largest measuring 2.7 X2.3 cm.

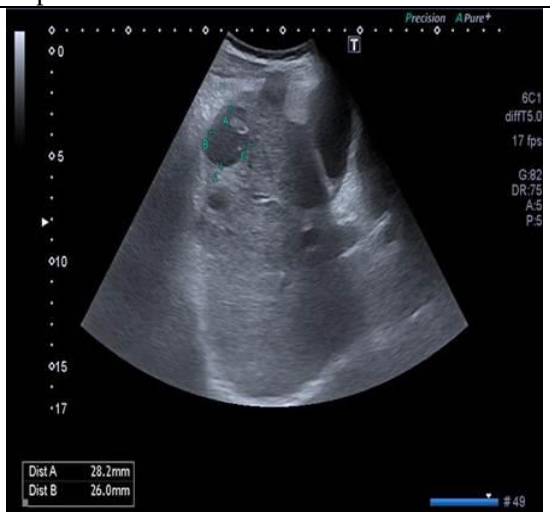
Shear wave sono-elastography stiffness values of the focal lesion (B, C):

Maximum stiffness = 59.7kPa, minimum stiffness = 32.9kPa, calculated average stiffness = 46kPa.

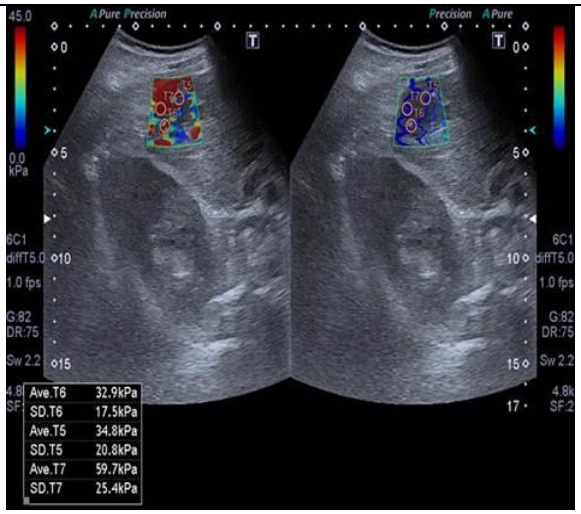
Axial contrast enhanced triphasic CT study, arterial (D), portal (E) & delayed (F) phases:

Cirrhotic liver with 3 focal lesions seen in segment VI displaying early arterial enhancement and delayed washout.

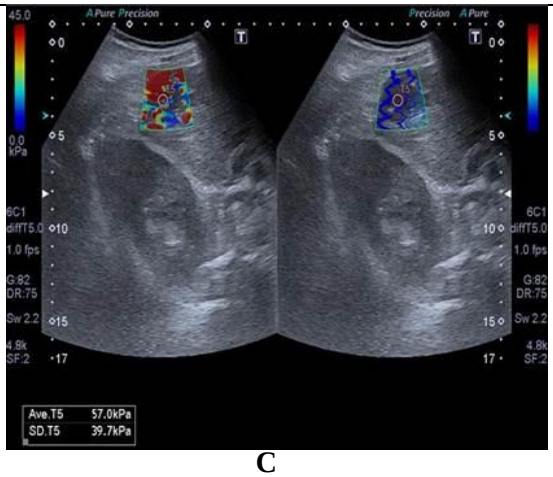
Diagnosis: Hepatocellular carcinoma.



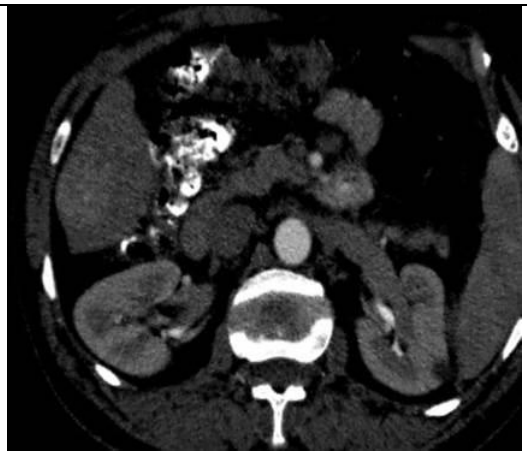
A



B



C



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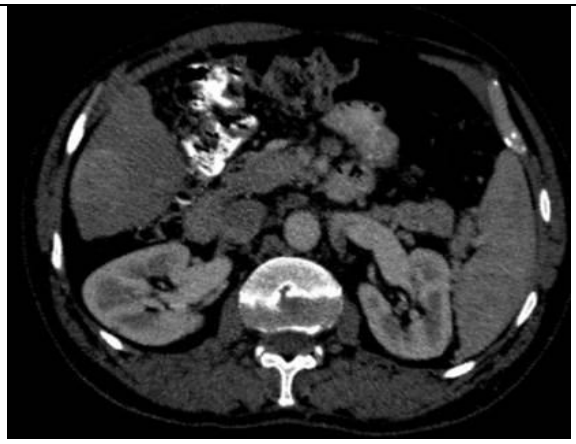
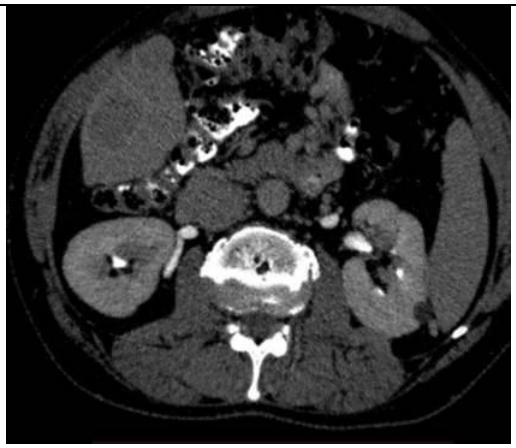


E



F

DISCUSSION

During abdominal ultrasonography, hepatic focal lesions are a common main issue. One of the most dangerous types of cancer is liver cancer malignant neoplasms worldwide. Liver cancer is the second leading cause of death in men and the sixth leading cause in women worldwide [11].

This cross-sectional study included 34 patients (23 males, 11 females) with hepatic focal lesions >1 cm, aged 22–68 years (mean 49.68 ± 9.73). Diabetes was present in 29.4%, smoking in 32.4%, and HCV in 35.4%. Of all patients, 13 had benign lesions (hemangiomas, focal fatty changes, adenoma & hemangiopericytoma) and 21 had malignant lesions (HCC, metastases & cholangiocarcinoma).

In the current study, when comparing the stiffness of benign and malignant lesions using SWE, there was a statistically significant difference (P<0.001) because the malignant lesions were more rigid than the benign ones, with mean value (30.9 KPa) for malignant focal lesions and (12.6 KPa) for benign lesions. This finding goes in agreement with **Gad *et al.*** [12] who used pointed SWE and reported that the comparison between benign and malignant lesions in terms of stiffness by SWE revealed a statistically significant difference (P<0.001) as malignant lesions demonstrated higher stiffness than the benign lesions. The median stiffness of metastatic focal lesions in this study was 4.83 kPa, which goes in agreement with **Hasab Allah *et al.*** [13] who reported 5.28 kPa as a median stiffness of metastatic focal lesions.

In the current study, there was no statistically significant difference between benign focal lesions in terms of their SWE stiffness values. These results are against with **Guibal *et al.*** [5] who reported that SWE mean stiffness value for the haemangiomas was 13.8 ± 5.5 and reported that FNH had significant differences in stiffness compared with adenomas (P = 0.0002). SWE was able to distinguish between cholangiocarcinomas and HCC in the current investigation. Compared to HCC, cholangiocarcinoma showed more stiffness, (30.28 ± 8.2 kPa vs. 84.2 ± 31.96 KPa) (P<0.001). This finding goes in agreement with **Gad *et al.*** [12] who reported that SWE was able to differentiate between HCC and cholangiocarcinoma, as there was statistically significant difference between the readings of the two groups (P value <0.05), with cholangiocarcinoma being more stiff than HCC.

In the current study, SWE was able to differentiate between HCC and focal fatty lesions (30.28 ± 8.2 kPa vs.10.42 ± 1.21 KPa) as focal fatty lesions demonstrated lower stiffness than HCC (P=0.017). This finding goes in agreement with **Gerber *et al.*** [4] who reported 9.8 kPa for focal fatty sparing (FFS) and reported 44.8 kPa for hepatocellular carcinoma. Given that the two groups' readings differed statistically significantly (P value <0.05) and that focal nodular hyperplasia (FNH) was stiffer than HCC, SWE was able to distinguish between the two conditions. This finding goes in agreement with **Gallotti *et al.*** [14] who reported a significant difference between SWE readings of HCC and FNH. Unfortunately, our study didn't includes cases of FNH.

In our study, SWE couldn't differentiates between HCC and (Metastases, hemangioma or adenoma and hemangiopericytoma). The comparison between hepatic lesions other than HCC revealed that cholangiocarcinoma demonstrated significantly higher stiffness than metastases, focal fatty lesions, hemangioma, adenoma and hemangiopericytoma (P<0.001). Moreover, focal fatty lesions had significantly lower stiffness than metastatic lesions (P=0.019). This finding goes in agreement with **Gad *et al.*** [12] who aimed to compare the stiffness of HCC with the stiffness of other hepatic focal lesions included in this study using SWE. Since there was no statistically significant difference between the two SWE readings, SWE was unable to distinguish between hemangioma and HCC groups (P value >0.05). This finding goes in agreement with **Hasab Allah *et al.*** [13] but on the contrary to **Park *et al.*** [15] who reported a significantly higher stiffness in HCC than in hemangioma.

In the current study, no correlation was detected between the stiffness and the size of HCC, localized and metastatic fatty lesions, and the size of the hemangioma was statistically significantly correlated with its mean stiffness value as determined by SWE (r=0.848, P=0.033). This partially agrees with a study by **Gad *et al.*** [12] in which No correlation was noticed between the elasticity of different focal lesions and their size and number. **Choong *et al.*** [16] revealed the same finding between the size of the lesion and its elasticity.

In the current study, at cut off point >18.6 KPs, the mean stiffness value measured by SWE could distinguish between benign and malignant lesions with a sensitivity of 95.24%, specificity of 84.62%, PPV of 90.9%, and NPV of 91.7% (AUC=0.886, P<0.001). While, in the study of **Park *et al.*** [15] the ROC curve showed that using a cut off value of 30.8 kPa with AUC 0.79, yielded 70.6% sensitivity and 82.4% specificity. This difference in accuracy may be attributed to that there was a sample size difference between the current study (34 lesions) and **Park *et al.*** [15] study (136 lesions).

LIMITATIONS

The study had a small sample size (34 cases), which may limit the statistical analysis. Certain lesions showed certain imaging features, however pathologic diagnosis was unavailable for some individuals. Additionally, the study included only one case of adenoma and one case of hemangiopericytoma, and no cases of focal nodular

hyperplasia were present.

CONCLUSION

SWE was able to differentiate between HCC and both cholangiocarcinoma, focal fatty findings as cholangiocarcinoma demonstrated higher stiffness than HCC, while focal fatty lesions (FFL) demonstrated lower stiffness than HCC. On the other hand, SWE couldn't differentiates between HCC and (metastases, hemangioma or adenoma and hemangiopericytoma). The comparison between hepatic lesions other than HCC revealed that cholangiocarcinoma demonstrated significantly higher stiffness than metastases, focal fatty lesions, hemangioma, adenoma and hemangiopericytoma. Moreover, focal fatty lesions had significantly lower stiffness than metastatic lesions. SWE offers additional characterization data for FLL interpretation and could be helpful, at the very least, in distinguishing between CCCs and HCCs.

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