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Role of transient elastography in the prediction of de novo recurrence of hepatocellular carcinoma after radiofrequency ablation: single-center Egyptian study

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Abstract

Background: Radiofrequency is one of the curative treatment options for hepatocellular carcinoma (HCC). Despite the progressive improvements in the efficacy of radiofrequency, the survival of patients with HCC who undergo radiofrequency remains disappointing, mainly due to frequent intrahepatic recurrence of HCC after radiofrequency. We aimed to evaluate the role of transient elastography (TE) in the prediction of de novo recurrence of HCC after radiofrequency and to compare between transient elastography and the serological fibrosis indices in the prediction of de novo recurrence of HCC.

Results: Thirty HCC patients underwent baseline transient elastography for preinterventional assessment of the degree of fibrosis. Also noninvasive serum fibrosis indices were calculated from baseline data, including age platelet index (API), cirrhosis discrimination score (CDS), and FIB-4 index. Patients achieving complete response after 1 month post radiofrequency ablation were followed for further 12 months by triphasic abdominal CT scan to detect de novo lesions according to modified RECIST criteria. Baseline means of CDS, FIB4, and API were 6.03 ± 1.5 , 3.98 ± 2.58 , and 1.24 ± 1.08 , respectively. Transient elastography revealed 28 patients with F4 and only 2 patients with F3 (mean liver stiffness 22.45 ± 10.36 Kba). There was a significant negative correlation between liver stiffness (LS) and de novo recurrence of HCC (mean of LS in patients with a complete response was 17.19 ± 3.32 while in those with de novo recurrence was 36.94 ± 5.93 , with the best cut off value ≥ 24.65 (p value < 0.001). There was no significant correlation between CDS, FIB4, API scores, and de novo recurrence of HCC. It was found that the liver stiffness was significantly associated with the prediction of hepatic decompensation (p value < 0.001). Also, liver stiffness at the cutoff value > 42.75 (p value = 0.031) was significantly associated with the prediction of 1-year mortality after radiofrequency ablation.

Conclusion: Our data suggested that liver stiffness measurement in hepatocellular carcinoma patients was a useful predictor of de novo recurrence, overall survival, and possibility of hepatic decompensation after radiofrequency ablation.

Keywords: Hepatocellular carcinoma, Radiofrequency ablation, Transient elastography, Noninvasive fibrosis indices, Liver stiffness, De novo recurrence of hepatocellular carcinoma

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Background

Liver cancer is considered the fifth most common cancer and also the second most frequent cause of cancer-related death globally. Hepatocellular carcinoma represents about 90% of primary liver cancers and constitutes a major global health problem [1].

In Egypt, HCC is a significant public health problem as it is responsible for 33.63% and 13.54% of all cancers in males and females respectively [2].

RFA has been accepted as an effective curative minimally invasive treatment modality for early-stage HCC tumors (solitary tumors 5 cm in diameter or fewer than 3 nodules, 3 cm in diameter) [3].

Intrahepatic recurrence of HCC after RFA is either local tumor progression or de novo recurrence. Local tumor progression results from direct dissemination of the original tumor along the peripheral margin of the ablated lesion, while de novo recurrence accounts for the multicenter occurrence of a HCC tumor in a location away from the ablated lesion [4].

Noninvasive fibrosis indices such as aspartate aminotransferase-to-alanine aminotransferase ratio (AAR), age-platelet index (API), cirrhosis discriminant score (CDS), and FIB-4 index can play an important role in the prediction of intra-hepatic distant recurrence (IDR) of HCC following percutaneous ablation [5].

Transient elastography is a noninvasive method that uses the measurements of liver stiffness (LS) to assess the degree of hepatic fibrosis in patients with chronic liver disease. It is easily performed, gives immediate results, and has good reproducibility [6]. In addition, TE is useful for predicting de novo recurrence of HCC in the remnant liver as well as survival after RFA [7].

We aimed to evaluate the role of transient elastography (as an indirect indicator for the degree of liver fibrosis) in the prediction of de novo recurrence of hepatocellular carcinoma after radiofrequency ablation in hepatitis C-related hepatocellular carcinoma and, in addition, to compare between transient elastography and other noninvasive fibrosis indices in the prediction of de novo recurrence of hepatocellular carcinoma after radiofrequency ablation hepatitis C-related hepatocellular carcinoma.

Methods

This prospective cohort study was conducted on 30 HCC patients attending the HCC outpatient clinics, Ain Shams University Hospitals, Cairo, Egypt. This study was held in the period between March 2017 and May 2019. All patients enrolled were HCV-related HCC (based on AASLD guidelines 2010), Child A class, with no previous management of HCC. All patients underwent baseline transient elastography (TE) for pre-interventional assessment of the degree of fibrosis (using

Echosense 502 Touch). Also noninvasive serum fibrosis indices were calculated from baseline demographic, biochemical, and radiological data, including age platelet index (API), cirrhosis discrimination score (CDS), and FIB-4 Index. Patients achieving complete response (CR) 1-month post RFA were followed for further 12 months. Triphasic abdominal CT scan was done at 1, 3, 6, and 12 months after intervention for the detection of any de novo lesions according to modified RECIST criteria (mRECIST). Written informed consent was obtained from all included patients. Treatment with DAAs was done according to the Egyptian guideline after curative treatment of HCC by RFA.

The exclusion criteria included other etiology of chronic liver disease rather than HCV, any patient not fit for RFA, previous management for HCC, refusal of being enrolled in the study, and previous treatment with DAAs before RFA.

Also all patients who did not achieve complete cure (according to mRECIST criteria) 1 month after RFA were excluded.

All patients were subjected to evaluation at baseline visit through medical history and clinical examination, investigations including CBC, liver profile, liver enzymes (ALT, AST), AFP, kidney function, and electrolytes and radiological assessment including pelvi-abdominal ultrasound and triphasic pelvi-abdominal CT scan, liver stiffness measurement using transient elastography 1 week before RFA. Age platelet index (API), cirrhosis discrimination score (CDS), and FIB-4 Index were calculated.

Treatment of HCC by RFA

RFA was carried out in the interventional radiology unit, Ain-Shams University Hospital using radionics cooled tip RF device and the session usually lasts from (12–15 min). It was performed percutaneously under ultrasound guidance. Patients should fast at least 6 h before the maneuver.

Follow up:

For all the patients who underwent RFA, the follow-up was done post maneuver at 1, 3, and 6 months and 1 year to determine the clinical outcome as tumor response according to the modified RECIST criteria (mRECIST) (complete response and recurrence), liver status, and survival. Only patients achieving CR 1-month post RFA were included and completed the follow-up for 12 months.

Laboratory investigations included CBC, liver function tests, liver enzymes, and AFP. The radiological investigations included (triphasic CT or dynamic MRI).

Ethical approval

This was done according to the regulations of the research ethical committee, Faculty of Medicine, Ain

Shams University. The number of the ethical approval is 137/2017 (2/4/2017).

Statistical analysis

The collected data was revised, coded, tabulated, and introduced to a PC using a statistical package for Social Science (SPSS 25). Data was presented and suitable analysis was done according to the type of data obtained for each parameter. The mean, standard deviation (\pm SD), and range were used to describe parametric numerical data, while the median and interquartile range (IQR) were used for non-parametric numerical data. Frequency and percentage were used to describe non-numerical data.

Chi-squared test was used in the comparison between two groups with qualitative data. Fisher's exact test was used to examine the relationship between two qualitative variables when the expected count is less than five in more than 20% of cells. The comparison between two independent groups with quantitative data and parametric distribution was done by using independent *t* test while the comparison between two groups with non-parametric data was done by using Mann-Whitney test. Multivariate analysis for the impact of HLA mismatch was assessed using the logistic regression model. *P* < 0.05, significant.

Results

The demographic data of the studied patients which shows that 66.7% of patients (20 patients) were males, 33.3% (10 patients) were females, the mean age was 57.07 years \pm SD, and 22 patients (73.3%) were from rural areas (data not shown). Baseline radiological assessment, liver stiffness, and noninvasive serological markers were shown in Table 1. Table 2 showed the laboratory investigations during 12 months of follow-up after RFA.

There was a significantly negative correlation between LS and de novo recurrence of HCC as shown in (Table 3) with the best cutoff value \geq 24.65 kPa (Fig. 1). There was no significant correlation between CDC, FIB4, API scores, and de novo recurrence of HCC (Table 3).

Table 4 shows the correlation between LS and FIB4 score and hepatic decompensation after 1 year of the first RFA. The means of LS and FIB4 in decompensated patients (in form of ascites and jaundice) were 38.53 ± 8.67 (*p* value <0.001) and 6.05 ± 4.71 (*p* value = 0.05), respectively.

LS can also predict the 1-year survival where there was a statistically significant correlation between LS and 1-year survival (*p* value <0.001) (Table 5) with the best cutoff value \geq 42.75 (Fig. 2).

Regarding the correlation between LS and the serological markers, there was a statistically significant

Table 1 Baseline radiological assessment, liver stiffness, and noninvasive serological markers

		Min.	Max.	Mean	SD
Spleen size (cm)		9.00	15.00	11.57	1.73
Largest lesion size (cm)		1.50	4.10	3.10	0.49
total tumor size (cm)		1.50	7.60	4.25	1.70
Liver stiffness (kPa)		11.80	46.40	22.45	10.36
CDS		4.00	9.00	6.03	1.50
FIB4		1.78	15.26	3.98	2.58
API		0.32	5.54	1.24	1.08
		N		%	
Fibrosis score	F3	2		6.7%	
	F4	28		93.3%	
Tumor number	1.00	19		63.3%	
	2.00	10		33.3%	
	3.00	1		3.3%	

The demographic data of the studied patients which shows that 66.7% of patients (20 patients) were males, 33.3% (10 patients) were females, the mean age was 57.07 years \pm SD, and 22 patients (73.3%) were from rural areas (data not shown). Table 1 showed the baseline radiological assessment, liver stiffness, and noninvasive serological markers of the included patients

correlation between LS and CDS, FIB4 score, and API, and the *p* values were 0.01, 0.01, and 0.02, respectively (Table 6) (Figs. 3, 4, and 5).

Discussion

Hepatocellular carcinoma is a major health problem especially in Egypt, where HCV appears to play a major role in the progression of chronic liver disease to HCC.

Radiofrequency ablation achieves a satisfactory local response rate, with more than 80% complete ablation in most studies, despite progressive improvements in the efficacy of RFA, the survival of patients with HCC who undergo RFA remains disappointing, mainly due to frequent intrahepatic recurrence of HCC after RFA.

The percentage of males in this study (66.7%) was higher than that of females (33.3%) with male to female ratio 2:1. An Egyptian study by Shaker et al [8] performed on 1313 patients with HCC revealed that the male to female ratio was 3.7:1.

Also, Hetta et al. [9] and Liu et al. [10] describe the male predominance of 81.9% and 92.5%, respectively.

High male to female liver cancer incidence rate ratios in some countries may reflect increased exposure of known risk factors amongst men. In Egypt, for example, the primary risk factor for liver cancer, hepatitis C viral infection, was widely transmitted by inoculations to control schistosomiasis, which was a disease more common amongst Egyptian men particularly those in rural areas who acquire it occupationally as farmworkers.

In this study, the age of patients ranged from 40 to 75 years with mean \pm SD 57.52 \pm 7.09 years. This finding is

Table 2 Laboratory investigations during 12 months of follow-up

	Base line		1 month		3 months		6 months		12 months		F	P
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Serum albumin (g/dl)	3.88	0.39	3.68	.34	3.59	0.37	3.49	0.46	3.33	0.55	23.21	<0.001
Total bilirubin (mg/dl)	1.14	0.41	1.17	0.47	1.21	0.53	1.30	0.62	1.42	0.78	320.90	<0.001
INR	1.11	0.12	1.16	0.14	1.20	0.14	1.64	0.91	1.26	0.19	1.25	0.29
ALT (u/l)	43.37	14.18	47.87	14.55	44.23	20.73	45.10	20.08	44.23	20.73	1.52	0.20
AST (u/l)	53.73	18.41	56.43	17.87	56.43	17.87	51.87	11.14	52.80	10.65	1.76	0.14
TLC (10 ³ /mL)	5.53	2.36	5.17	2.14	5.04	1.92	5.18	2.18	4.84	1.92	1.71	0.15
HB (g/dl)	11.95	1.33	11.75	1.30	11.46	1.13	11.27	1.22	11.17	1.27	13.15	<0.001
Platelets (10 ³ /mL)	147830	51700	143830	47380	139730	50330	135800	49750	128730	50.00	7.72	<0.001
BUN (mg/dl)	16.07	6.93	16.83	7.29	17.87	7.61	15.63	5.77	18.73	7.39	1.68	0.16
CR (mg/dl)	0.92	0.19	0.97	0.20	0.99	0.24	1.00	0.26	1.08	0.33	4.004	0.004
NA (meq/l)	136.67	2.09	136.40	2.46	135.50	3.15	134.77	3.45	133.83	5.75	6.33	<0.001
k (meq/l)	4.11	.32	4.04	.31	3.85 ^b	.27	3.86	.35	3.77	0.44	8.75	<0.001
*AFP (ng/dl)	42.00	54.00	8.50	6.00	6.50	6.00	6.30	5.00	6.05	59.00	51.64	<0.001

*Median and IQR

close to Hussein et al. [11], who reported that the age of patients with HCC was 40–77 years with a mean of 56 ± 8.15 years.

In another Egyptian study by Shaker et al. [8], they found that the most frequent age group affected by HCC was between 51 and 60 years (45.7%), followed by the group between 41 and 50 years (24.4%). Also Hetta et al. [9] reported the mean age of HCC was 57 ± 4.6 years.

Relatively younger age in the Egyptian patients can be explained by the high prevalence of HCV among Egyptians and the occurrence of the infection at a young age.

In the current study, it was found that there was a significant negative correlation between LS measurement by TE and de novo recurrence of HCC with the mean of LS in patients with a complete response was (17.19 ± 3.32 kPa) and the mean of LS in patients with de novo recurrence was 36.94 ± 5.93 kPa), with the best cutoff value of LS to predict de novo HCC recurrence after RFA a value of (\geq 24.65 kPa).

Conti et al. [12] reported that HCC recurrence more significantly recognized in the patients with LSM values over 21.5 kPa before DAA therapy.

Different results were described by Lee et al. [7] who adopted a LS cutoff value of 13.0 kPa to determine the high-risk group for recurrence.

Also Jung et al. 2012 [13] found that HCC patients with preoperative LS values more than 13.4 kPa experienced a higher incidence of HCC recurrence after curative resection than did their counterparts.

As regards the differences in the cutoff value, this phenomenon can be explained in several ways. First, in the different etiologies of CLD in the studies population, we avoided this obstacle by excluding other etiologies rather than HCV in our sample and also the duration of the follow-up, with a higher possibility of recurrence with a long duration of follow-up even with low LS.

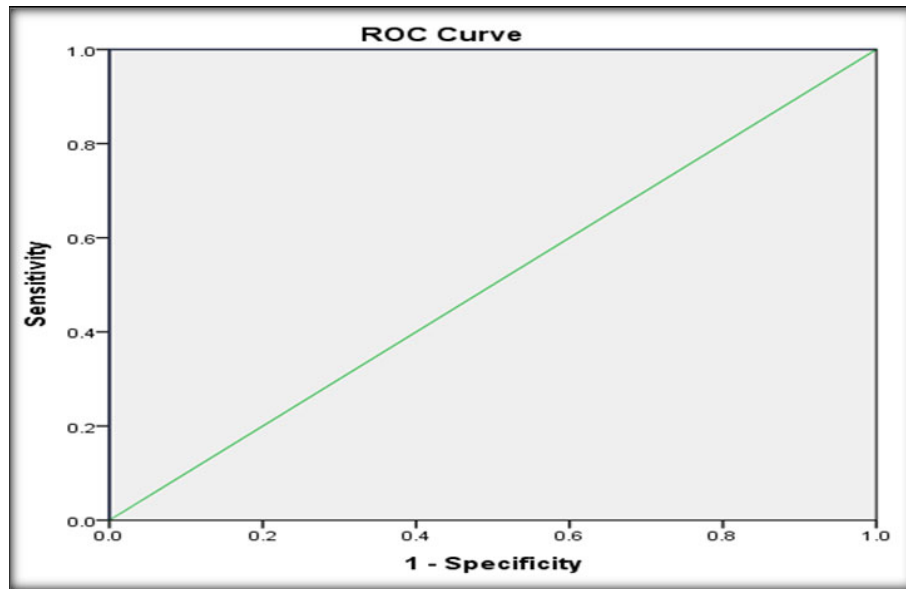
In the present study, we found that the LS was significantly associated with the prediction of hepatic decompensation after RF. The LS mean in patients

Table 3 Relation between de novo HCC recurrence and noninvasive liver fibrosis tests

	Response after 1 year				t*	P value
	Complete response (n=22)		De novo recurrence (n=8)			
	Mean	SD	Mean	SD		
LS	17.19	3.32	36.94	9.20	5.93	<0.001
CDS	5.77	1.34	6.75	1.75	1.63	0.12
FIB4	3.39	.98	5.60	4.54	1.36	0.21
API	1.02	.65	1.82	1.73	1.27	0.24

*Student t test

There was a significantly negative correlation between LS and de novo recurrence of HCC with best cutoff value \geq 24.65 kPa (Fig. 1). There was no significant correlation between CDS, FIB4, API scores, and de novo recurrence of HCC



The best cut off value was ≥ 24.65

Sensitivity = 100%

Specificity = 100%

Fig. 1 Validity of LS measurement in prediction of recurrence after 1 year. The best cutoff value was ≥ 24.65 , sensitivity = 100%, and specificity = 100%

without any manifestation of hepatic decompensation after RF was 17.3 kPa, patients complicated by with ascites only their LS mean was (23kPa), while those who were complicated by both ascites and jaundice during the period of follow-up was (38.5kPa) (p value < 0.001).

Also Kang et al. [14] suggested that patients with higher LS values (13–18 and ≥ 18 kPa) had significantly higher risks of developing hepatic decompensation after RF compared to those with lower values (< 13 kPa) (HR = 4.547, $P = 0.044$ and HR = 12.446, $P < 0.001$, respectively).

A prospective study by Robic et al. [15] demonstrated that a preoperative LS > 21.1 kPa proved as effective as hepatic venous pressure gradient measurements to predict the clinical decompensation and liver-related events (ascites, variceal bleeding, HCC, HE, and death) after curative resection.

Two studies also looked at the evolution of liver stiffness values over time (Corpechot et al. [16], Vergniol et al. [17]) and found that patients with increasing liver stiffness (1–1.5 kPa per year) were a higher risk of developing complications, with one study estimating a 10-fold increase in complications (Corpechot et al. [16]).

Table 4 Relation between liver decompensation and noninvasive liver fibrosis tests

	Decompensation after 1 year						F*	P value
	No decompensation (n=22)		Ascites only (n=1)		Ascites and jaundice (n=7)			
	Mean	SD	Mean	SD	Mean	SD		
LS	17.31	3.59	23.00	.	38.53	8.67	44.70	< 0.001
CDS	5.73	1.35	6.00	.	7.00	1.73	2.06	0.15
FIB4	3.36	1.00	3.09	.	6.05	4.71	3.42	0.05*
API	1.02	0.65	1.02	.	1.96	1.82	2.22	0.13

*One-way ANOVA test

Table 5 Relation between 1-year survival and noninvasive liver fibrosis tests

	Survival at 1 year				t*	P value
	Alive		Died			
	Mean	SD	Mean	SD		
LS	20.84	8.66	45.00	.00	3.88	<0.001*
CDS	5.96	1.50	7.00	1.41	0.94	0.35
FIB4	3.97	2.67	4.15	1.15	0.09	0.93
API	1.22	1.11	1.42	0.41	0.25	0.81

LS can also predict the 1-year survival where there was a statistically significant correlation between LS and 1-year survival (p value <0.001) with the best cutoff value ≥ 42.75 (Fig. 2)

In the present study, we found that the LS at cutoff value >42.75 (p value = 0.031) and splenomegaly above 12.93 cm (p value <0.021) were significantly associated with the prediction of the 1-year mortality after RFA.

Lee et al. [7] founded that on univariate analysis, total bilirubin, spleen size, and LS value 13.0 kPa significantly predicted overall survival after RFA (all p value=0.05).

Pang et al. [18] found that among 2052 patients (with median age 51 years, 65% with hepatitis B or C), 87 patients (4.2%) died or developed a hepatic complication during a median follow-up period of 15.6 months (interquartile range, 11.0–23.5 months). Patients with complications had higher median liver stiffness than those without complications (13.5 vs. 6.0 kPa; $P<0.00005$). The 2-year incidence rates of death or hepatic complications were 2.6%, 9%, 19%, and 34% in patients with liver

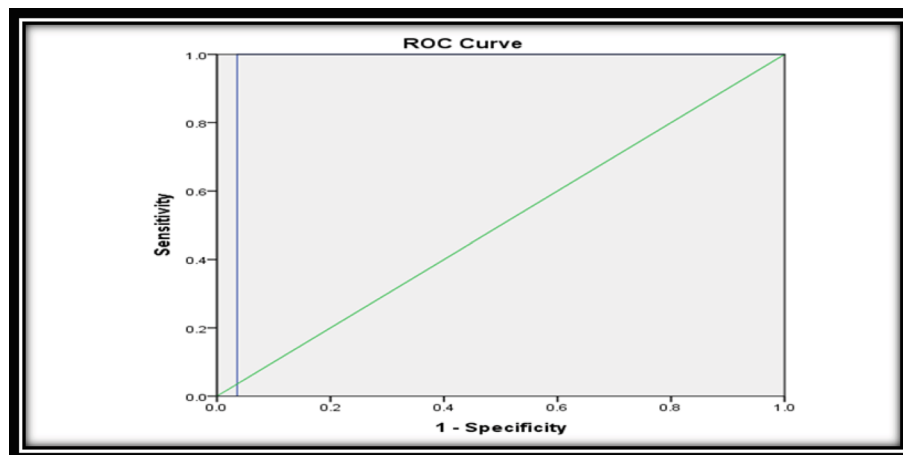
stiffness <10, 10–19.9, 20–39.9, and ≥ 40 kPa, respectively ($p<0.00005$)

In our study, it was found that there was no statistically significant correlation between FIB4 index, CDS, and API and de novo recurrence of HCC.

That phenomenon was also observed in a study by Suh et al. [19], suggesting that FIB-4 has the limited capability in differentiating the risk of HCC development in contrast to LS.

Also Kim et al. [20] LS reported that TE showed significantly greater prognostic performance than FIB-4 in predicting the development of HBV-related HCC. The combined use of LS and FIB-4 did not provide additional benefit compared with the use of LS alone.

Seo et al. [5] found that FIB-4 was not significantly correlated with Intrahepatic distant recurrence after



The best cut off value ≥ 42.75

Sensitivity = 100%

Specificity = 96.4%

Fig. 2 Validity of LS measurement in prediction of death after 1 year. The best cutoff value ≥ 42.75 , sensitivity = 100%, and specificity = 96.4%

Table 6 Correlation between noninvasive liver fibrosis tests

	LS	
	r*	P value
CDS	0.49	0.01
Fib4	0.48	0.01
API	0.44	0.02

r* (Pearson's test)

Regarding the correlation between LS and the serological markers, there was statistically significant correlation between LS and CDS, FIB4 score and API, p values were 0.01, 0.01, and 0.02, respectively

RFA of hepatitis B-related HCC in contrast to CDS and API which had a significant correlation with intrahepatic distant recurrence with (p values 0.010 and 0.004), respectively.

The current study shows the correlation between baseline FIB4 score and the occurrence of hepatic decompensation after 1 year of intervention. The mean

of FIB4 score in patients complicated by ascites and jaundice was 6.05 ± 4.71 (p value 0.05).

Butt et al. [21] concluded that FIB-4 was superior to the Child-Pugh and MELD scores for prediction of incident hepatic decompensation and hepatocellular carcinoma events among chronic HCV-infected persons. At a FIB-4 cutoff score of three, less than 1% of chronic HCV-infected patients developed hepatic decompensation or hepatocellular carcinoma.

Conclusion

In conclusion, patients with higher LS values than the cutoff value of 24.65 kPa were at a significantly higher risk for de novo recurrence of HCC after RFA. In addition, patients with LS cutoff value ≥ 42.75 kPa experienced significantly decreased overall survival after RFA and increased risk of post interventional hepatic decompensation. Also there was a correlation between baseline

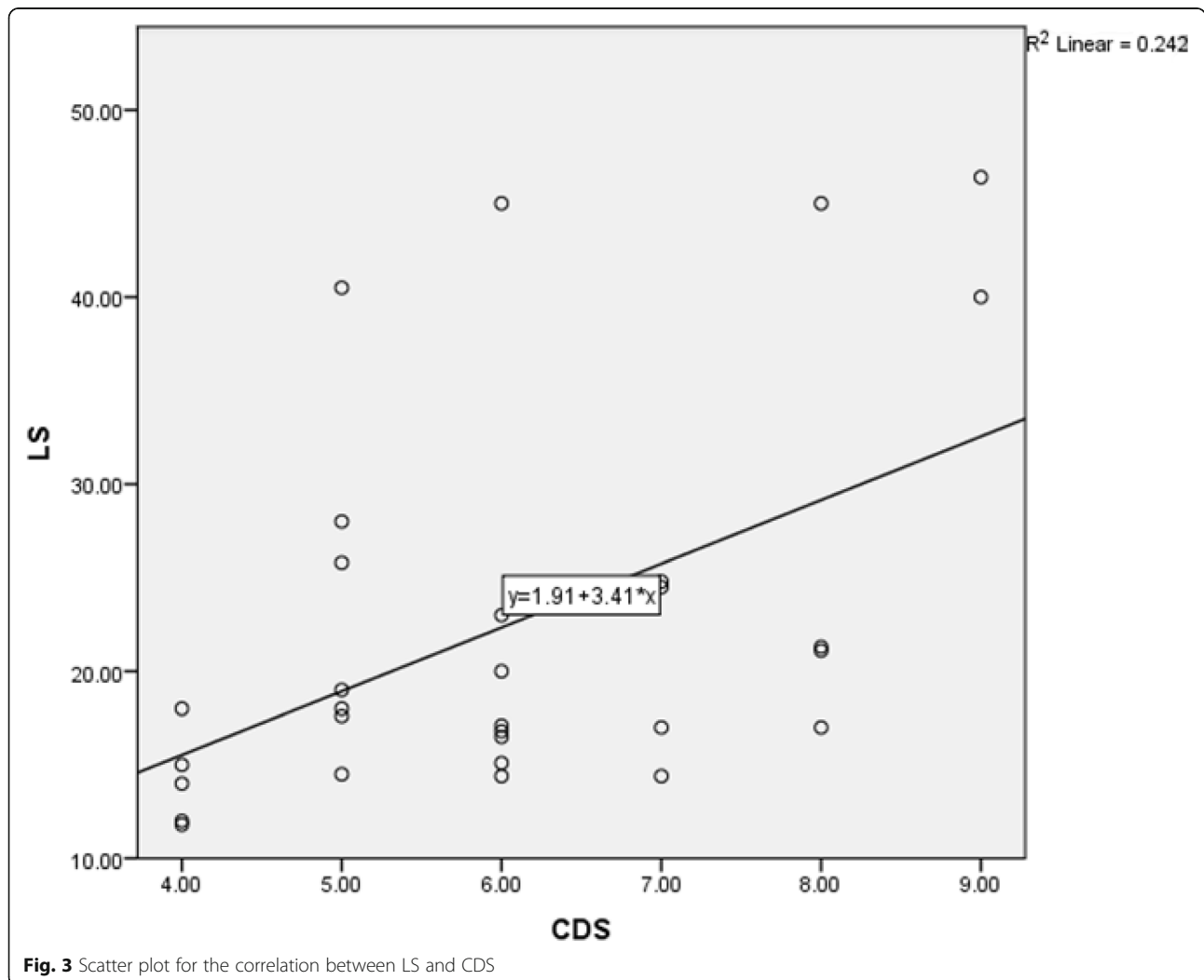


Fig. 3 Scatter plot for the correlation between LS and CDS

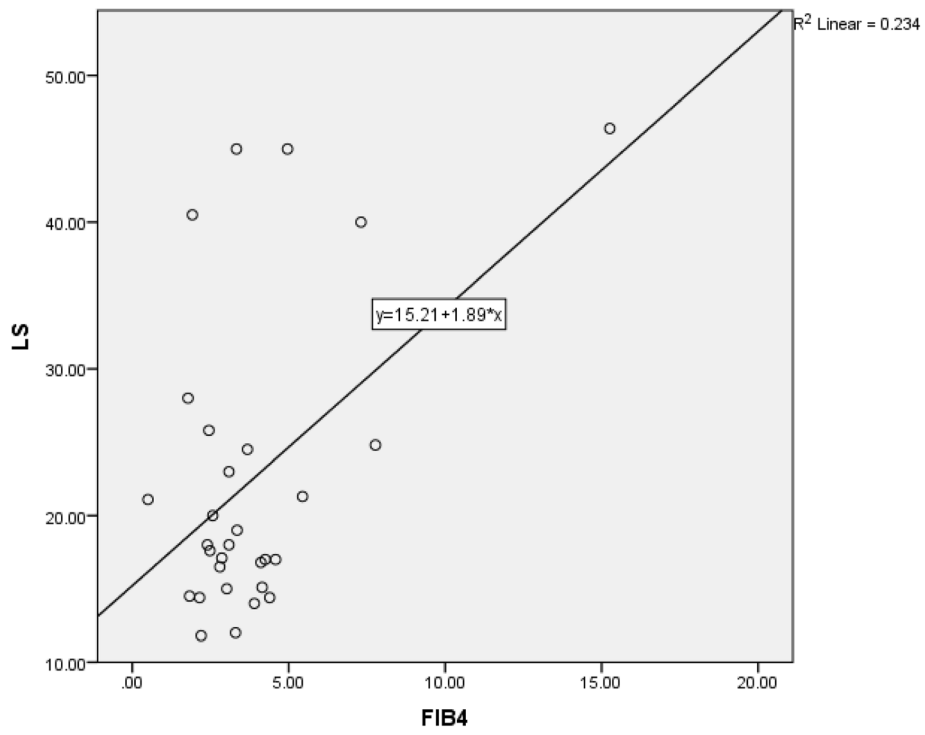


Fig. 4 Scatter plot for the correlation between LS and FIB4

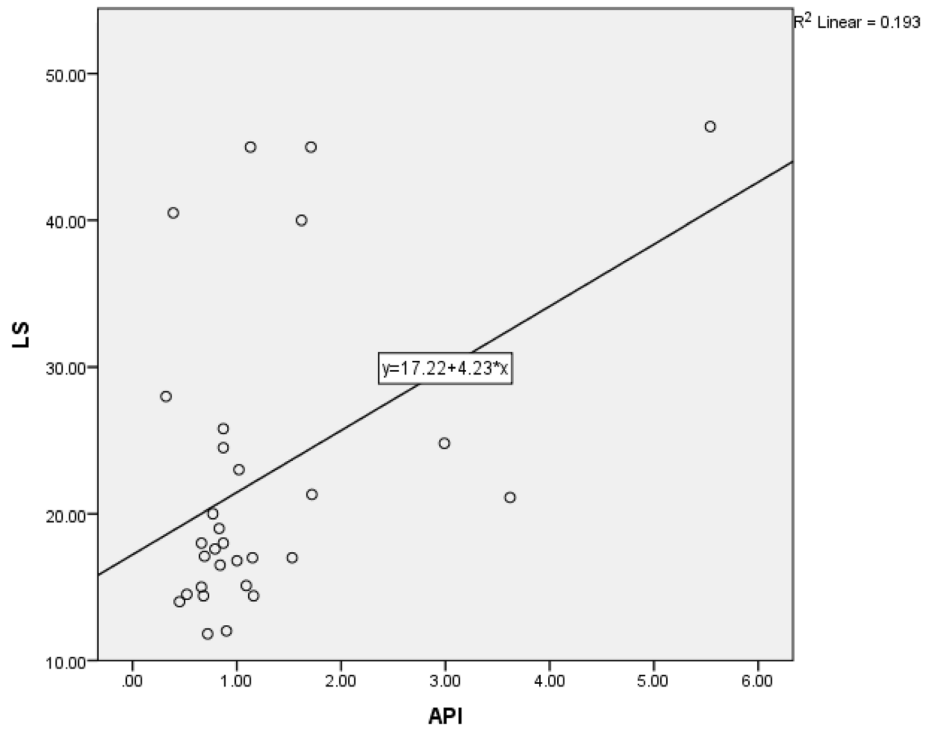


Fig. 5 Scatter plot for the correlation between LS and API

FIB4 score and the occurrence of hepatic decompensation during 1 year of follow-up after an intervention.

Limitations of the study Although our study indicates that LS measurement by using transient elastography is useful for predicting de novo recurrence of HCC in the remnant liver as well as survival after RFA, external validation of our results in future large-scale prospective studies can expand the clinical implications of TE in a longitudinal perspective.

Abbreviations

HCC: Hepatocellular carcinoma; RFA: Radiofrequency ablation; LS: Liver stiffness; Fib4: Fibrosis 4; CDS: Cirrhosis discrimination score; API: Age-Platelet Index; mRECIST: Modified response evaluation criteria in solid tumors

Acknowledgements

Not applicable

Ethical approval and consent to participate

Written consent was taken from each patient who agreed to participate in the research process. The agreement for participation of the subjects was taken after the aim of the study has been simply explained to them prior to data collection. They were assured that anonymity and confidentiality would be guaranteed and about their right to withdraw from the study at any time without giving any reason. Values, culture, and beliefs were respected. This was done according to the regulations of the research ethical committee, Faculty of Medicine, Ain Shams University. The number of the ethical approval is 137/2017 (2/4/2017).

Consent for publications

Informed consent to publish patients' data was signed by all participants prior to the beginning of the research.

Declarations

Authors' contributions

NA performed the fibroscan for all of the patients.
SA and HA collected the data and followed-up the patients.
MG performed RFA for all patients.
MH analyzed the data.
HA revised all the data and wrote the manuscript.
The authors have read and approved the manuscript.

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Availability of data and materials

The authors confirm that the data supporting the finding of this study are available within the article.

Competing interests

The authors declare that they have no competing interests.

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