



Prognosis value of liver stiffness measurements by 2D-SWE in primary HBV-positive hepatocellular carcinoma following radiofrequency ablation

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Background: Liver fibrosis is closely associated with the occurrence of hepatocellular carcinoma (HCC), which can be evaluated by liver stiffness measurements (LSM). The clinical significance of LSM in patient with hepatitis B virus (HBV) related HCC underwent radiofrequency ablation (RFA) was evaluated.

Methods: Total of 273 patients underwent RFA for primary HBV-positive HCC were included. LSM values were measured by using by 2D-shear wave elastography (2D-SWE) prior to RFA. The relationship between pretreatment LSM value and survival outcome was evaluated. The cutoff value for LSM to predict survival outcome was determined by receiver operating characteristic (ROC) curve analysis.

Results: At the endpoint of this study, 88 (32.2%) and 73 (26.7%) patients out of all 273 patients studied had died and recurrent, respectively. All patients were divided into two groups based on the cutoff value (13.4 kPa) of LSM. Patients with a LSM \geq 13.4 kPa had lower mean overall survival (62.5 vs. 48.5 months, $P=0.01$) and lower recurrent free survival (60.4 vs. 47.3 months, $P=0.02$) than patients with a LSM $<$ 13.4 kPa in univariate analysis and LSM also been evaluated as independent predictive factor for survival outcome for HCC following RFA. Otherwise, LSM also was related to liver cirrhosis and TNM stage (both $P<0.05$).

Conclusions: LSM measured by 2D-SWE can serve as an independent prognostic indicator for patients undergoing RFA for HBV-positive HCC.

Keywords: Liver stiffness; radiofrequency ablation; hepatitis B virus (HBV); hepatocellular carcinoma (HCC); prognosis

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Introduction

Hepatocellular carcinoma (HCC) is claimed to be one kind of the most common malignancy in background with a high morbidity of hepatitis virus infection, which is also the third commonest cause of cancer-associated mortality in China for its aggressive recurrence and metastasis (1-4). Despite advancement of adjunctive treatment, surgery and transplantation have taken benefits for HCC patients over decades, the survival outcome of HCC still be unsatisfactory

with main contributors of relapse or metastasis, especially for patients complicated with severe cirrhosis (5-7). Radiofrequency ablation (RFA) has been developed as an effective treatment approach for HCC patients with severe cirrhosis, which also had benefits in terms of complications and hospitalization duration (8-10). HBV infection related liver fibrosis or cirrhosis has been confirmed as a significant factor relating to prognosis of HCC (11-13). Thus, accurately quantitative evaluation of the fibrosis is crucial for

evaluating prognosis and furtherly guiding satisfaction of HCC patients. Moreover, stratification of patients according to biomarkers is crucial for individualized treatment and prognostic prediction, such as Child–Pugh score and Model for end-stage liver disease (MELD) score (14,15). However, in clinical, liver fibrosis mainly is assessed through liver biopsy or postoperative histological examination, which is characterized by invasive, risk of complications and diagnostic bias (16–18). So non-invasive novel methods of pretreatment fibrosis measurement are required.

Recently, liver stiffness measurement (LSM) via 2D-shear wave elastography (2D-SWE) has been showed as a reproducible, reliable and common method for liver fibrosis evaluation (19–22). LSM is also used to predict the occurrence of HCC in chronic liver disease patients (23,24). Furthermore, LSM can be used to predict postoperative complication and relapse in HCC patients underwent surgical resection (25–27). However, the significance of LSM measured by 2D-SWE in prediction of survival and clinical staging of HBV positive HCC patients underwent RFA has not been fully and clearly elucidated. Hence, we try to evaluate significance of LSM measured by 2D-SWE in prognosis evaluation for patients underwent RFA for HBV positive HCC.

Methods

Patients

Ethics approval of this study was obtained from the Institutional Review Board of the First Affiliated Hospital of Anhui Medical University, which was also conducted by adhering to the declaration of Helsinki and corresponding guidelines, all subjects were required for written informed consent. Two hundred seventy-three patients with primary single HCC undergone RFA at the First Affiliated Hospital of Anhui Medical University between June 1, 2013 and June 1, 2018 were included in this study. All patients were confirmed as single HCC with HBsAg positive prior RFA. Inclusion criteria included the largest diameter of HCC no more than 5cm, no distant metastasis, no portal vein tumor thrombus and micro-vessels invasion, Child-Pugh level A or B, incomppliance to surgery. Patients with severe preoperative infection, malignant hematologic disease, metastatic cancer, other malignancies were excluded. Patients with unavailable and unreliable clinicopathologic data and 2D-SWE measurement and received preoperative adjuvant treatments were also excluded. Clinicopathologic

information of all patients were collected, including gender, age, tumor size, liver status, Child-Pugh stage, HBsAg, AFP level, bilirubin, creatinine, international normalized ratio (INR), sodium level, tumor size, and laboratory tests. Histopathological staging was assessed by histopathological study. Pre-RFA bilirubin, creatinine, INR, and sodium level were used to calculate MELD scores.

RFA procedure

Fasting for at least 4–6 hours before RFA for all patients. Following conscious sedation and local anesthesia, RFA procedures were conducted percutaneously under ultrasound (US) guidance. Each tumor was ablated by twice to four times overlapping insertions of single electrode with a 3.5-cm exposed tip (ValleyLab, Burlington, MA). Full ablation was defined as the ablation area overlapping over 1.0 cm width margin of the normal liver parenchyma near the HCC. US was applied to evaluate and observe ablation area in real time. When the ablation area overlapped 0.5–1.0 cm width margin beyond entire HCC, the ablation was finished. After the electrode withdrawn, the needle track was routinely cauterized to avoid tumor seeding and bleeding.

LSM by 2D-SWE

All patients underwent LSM examination immediately prior to RFA treatment. Aixplorer ultrasound system (Supersonic Imagine, France) with a convex broadband probe (SC6-1, 1–6 MHz) was used to perform LSM measurement by 2D-SWE technology in accordance with the manufacturer's instructions. All LSM measurements were conducted by one experienced sonographer blind to the patients' information. Patients were placed in a supine position with the right arm in maximum abduction, and expose right intercostal space for scanning right liver lobe. Valid LSM was defined as 10 effective measurements for each patient. The result of LSM was expressed as the mean (M) of effective measurements in kilopascals (kPa). The Sonographer were blinded to all data of patient.

Outcome evaluation

All patients were followed up by outpatient visiting or telephone visiting in a regular interval frequent. Enhanced imaging evaluations were usually conducted every 12 months. Clinical following-up periods lasted from the day of surgery to either the day of death or May

Table 1 Baseline characteristics of 273 HCC patients treated by RFA

Characteristics	All patients (n=273)
Demographic factors	
Age, years	58.2±2.1
Male	172 (67.9%)
BMI, kg/m ²	25.5±3.1
Liver cirrhosis	185 (67.7%)
Child–Pugh class, A/B	190 (69.6%)/82 (30.4%)
MELD scores	17.9±9.4
Tumor factors	
Tumor size, cm	2.9 (1.4–5.0)
Alpha-fetoprotein, ng/mL	22.7 (1.2–3,100.0)
Laboratory tests	
Alanine aminotransferase, IU/L	35.4±21.5
Albumin, g/L	38.3±5.7
Total bilirubin, mg/dL	0.87±0.43
Platelet count, 10 ⁹ /L	124±62
Prothrombin time, INR	1.08±0.11
Noninvasive fibrosis measurement	
LSM, kPa	13.6 (4.3–46.2)
Patients with an LSM ≥13.4 kPa	187 (68.5%)

HCC, hepatocellular carcinoma; RFA, radiofrequency ablation; BMI, body mass index; LSM, liver stiffness measurement; MELD, model for end-stage liver disease scores.

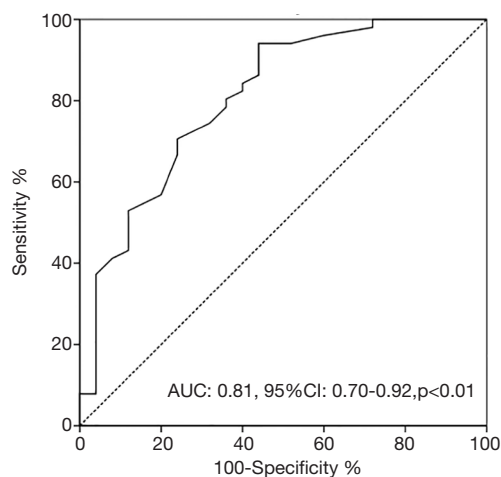


Figure 1 Receiver-operator characteristic curve for LSM measured by 2D-SWE. the AUC were 0.81 with a 95% CI between 0.70 and 0.92, $P < 0.01$.

2019. Overall survival (OS) was evaluated as the primary outcome of this study, which was defined as the period from date of RFA to time of disease-specific death. The secondary outcome was the Recurrent-free survival (RFS). Recurrences were consisted of intrahepatic local recurrence, extrahepatic recurrence and intrahepatic distant recurrence.

Statistical analysis

Statistical analyses were conducted by using the SPSS 20.0 (IBM, USA). $P < 0.05$ (two sided) was confirmed as statistically significant. The optimal cutoff value of the LSM to predict survival was determined by receiver operating characteristic (ROC) curve analysis. The association between qualitative variables and LSM was analyzed by using the χ^2 test or Fisher's exact test, whereas the association between LSM quantitative values was evaluated by independent student's t -test. The OS and RFS and survival curve were analyzed in the Kaplan-Meier analyses by using the log-rank test. The Cox regression model was applied to evaluate the hazard ratio (HR) and to conduct multivariate analysis.

Results

Baseline clinical and pathological characteristics

Baseline characteristics of 273 primary HCC patients enrolled in this study were shown in *Table 1*. There were 168 males and 95 females in whole group of HCC patients, with 58.2±2.1-year average age. A total of 185 (67.6%) patients had liver cirrhosis. The most (190, 69.6%) of all patients had a Child–Pugh class A liver function. Among the whole group of HCC patients. Otherwise. Median preoperative LSM measured by 2D-SWE was 13.6 (4.3–46.2) kPa, which was positively significantly related to liver cirrhosis (both $P < 0.05$, by χ^2 test).

Prognostic value of LSM for OS of HCC after RFA

Based on the results of ROC curve analysis, An LSM measured by 2D-SWE of 13.4 kPa (AUC, 0.81; 95% CI: 0.70–0.92; $P < 0.01$) was confirmed as the cutoff level predicting survival outcome, with a sensitivity of 91.4% and a specificity of 65.2%, respectively (*Figure 1*).

At the endpoint (mean 36.6±12.3 months), 88 (32.2%) out of all 273 patients had died. In 82 patients with an LSM level measured by 2D-SWE less than 13.4 kPa, 19 (23.2%) patients died, with an estimated mean overall survival of

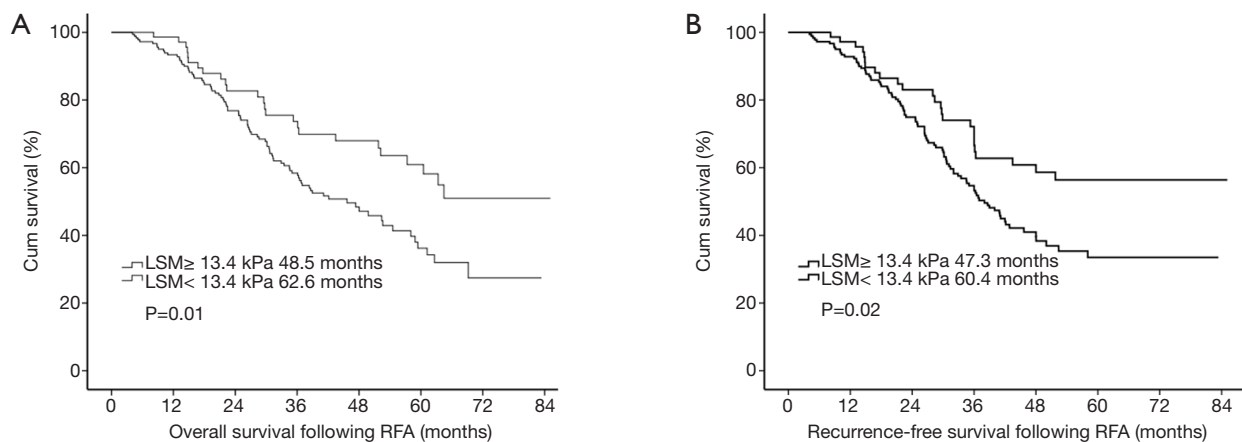


Figure 2 Kaplan–Meier estimates of survival. (A) Patients with a high LSM level had a poorer OS than those with a low LSM level (62.5 vs. 48.5 months, $P=0.01$). (B) Patients with a high LSM level had a poorer OS than those with a low LSM level (60.4 vs. 47.3 months, $P=0.02$).

62.6 months. Among 191 patients with an LSM values ≥ 13.4 kPa, 66 (34.6%) patients died, with an estimated mean overall survival of 48.5 months. The difference of mean OS between groups was statistically significant (hazard ratio, 5.12; 95% CI: 1.38–16.52; $P=0.01$, *Figure 2A*, *Table 2*).

Multivariate analysis enrolled age and sex of patients, BMI, liver cirrhosis, tumor size, MELD scores, laboratory tests and LSM measured by 2D-SWE into the COX regression model, which showed that LSM ≥ 13.4 kPa (hazard ratio, 3.88; 95% CI: 1.26–9.35; $P<0.01$) remained the independent risk factor of OS (*Table 2*).

Prognostic value of LSM for RFS of HCC after RFA

Among 273 HCC patients successfully treated by RFA, recurrent developed in 73 (26.7%) patients. Fifty-six (29.3%) in group of 191 patients with an LSM ≥ 13.4 kPa had tumor recurrent whereas 13 (15.9%) in 82 patients with an LSM < 13.4 kPa had a recurrence. In univariate analysis, patients with a high LSM level had a poorer mean RFS than those with a low LSM (60.4 vs. 47.3 months, $P=0.02$), and the LSM ≥ 13.4 kPa also was an independent risk factor for RFS of HCC patients in multivariate analysis (HR, 2.87; 95% CI: 1.03–9.15; $P<0.01$) (*Table 3*, *Figure 2B*).

Discussion

Liver fibrosis has been considered as a significant contributor to progression and metastasis of HCC, especially for patients complicated HBV infection (28–30). In present study, we showed that the LSM value measured

by 2D-SWE was an independent prognostic indicator for HBV positive HCC patients underwent RFA. Moreover, we also found that LSM level was significantly associated with liver cirrhosis, thereby concluded that advanced tumor tends to have a high liver stiffness. Furthermore, patients with a high LSM had significant poorer RFS than those with a low LSM, indicating that LSM can not only be applied to evaluate survival, but also the risk of recurrent.

Liver fibrosis acts as a healing response in setting of chronic liver injury, which may chronically lead to liver cirrhosis, thereby severing as a contributor to the development of HCC (31,32). Previously, the extent and degree of liver fibrosis has usually been assessed by tissue pathological examination (33,34). However, there are several limitations in effective of pathological evaluation of liver fibrosis, such as unsatisfied accuracy due to both sampling variability and inter-observer variability depend on pathologists, invasive procedure potentially causing risk of complications (35,36). Therefore, several effective noninvasive methods for liver fibrosis evaluation have been published. Until now, LSM, also referred to transient elastography, has been considered as the most widely used measurement to assess liver fibrosis (37).

The diagnostic and prognostic values of LSM by 2D-SWE for liver fibrosis of patients with chronic HBV infection have been extensively evaluated and validated (38–40). For patients with HBV positive HCCs, the presence of liver fibrosis is a well-known risk factor for both the development of post-treatment liver failure and prognosis (15,41). Therefore, considering the results of previous studies and current study, it is possible that the

Table 2 Univariate and multivariate analyses of the prognostic indicator of OS for HCC following RFA

Variables	Univariate			Multivariate		
	HR	95% CI	P	HR	95% CI	P
Demographic factors						
Age ≥ 55 years	1.01	0.82–1.63	0.21			
Sex (male)	0.67	0.53–2.86	0.42			
BMI ≥ 25 kg/m ²	1.11	0.78–2.62	0.17			
Liver cirrhosis	2.53	0.96–8.76	0.08			
Child-Pugh stage	1.42	0.46–4.21	0.47			
MELD scores	2.17	1.12–4.18	0.02	1.87	1.01–3.56	<0.01
Tumor factors						
AFP (ng/mL)	1.01	0.98–1.03	0.07			
Tumor size (cm)	1.61	0.83–2.77	0.63			
Laboratory tests						
ALT	2.17	0.98–9.63	0.51			
ALB	0.67	0.13–1.94	0.32			
TB	3.88	1.12–9.37	0.03	3.16	1.25–8.62	0.03
PLT	1.00	0.99–1.01	0.06			
PT	1.01	0.99–1.03	0.21			
Fibrosis status						
LSM ≥ 13.4 kPa	5.12	1.38–16.52	0.01	3.68	1.22–9.86	<0.01

OS, overall survival; HCC, hepatocellular carcinoma; CI, confidence interval; HR, hazard ratio; BMI, body mass index; AFP, alpha-fetoprotein; ALT, alanine aminotransferase; ALB, albumin; TB, total bilirubin; PLT, platelet count; PT, prothrombin time; LSM, liver stiffness measurement; MELD, model for end-stage liver disease scores.

poorer survival of HCCs following RFA in patients with a higher LSM value could be partly due to the presence of liver fibrosis. Therefore, LSM might serve as a valuable noninvasive predictor for prognosis of liver cancer. In previous studies, the most optimal cut-off level of LSM for liver cirrhosis diagnosis was 11.8–15.9 kPa in the HBV and HCV cases (42–44). However, the optimal cut-off level for liver stiffness associated with HCC remains undefined. Previous study showed that chronic hepatitis B patients with a LS value >12 kPa had an observable higher risk of HCC development (24). In addition, HCC patients with a pretreatment LSM value >13 kPa or 13.4 kPa suffered from a higher rate of recurrent (26,45). Optimal cut-off levels were often calculated by using a common analysis of ROC curve. In our study, the optimal cut-off level of LSM predicting survival of HCC following RFA was 13.4 kPa, which was consistent with previous studies. We further

confirmed the validity of this cut-off level in recurrent of HCC after RFA.

In this study, LSM value significantly related to liver cirrhosis. However, the LSM level was significantly correlated to prognosis of HCC after RFA whereas presence of liver cirrhosis was not an independent factor for OS and RFS. In clinical practice, liver cirrhosis was usually evaluated by ultrasonography, histological evaluation and imaging, but its severity cannot be quantitatively evaluated (46). LSM value can be used to detect compensated liver cirrhosis in an accurate style and expressed as continuous quantitative values, which also can overcome ultrasound doctor dependent limitation (47). Furthermore, it has been showed that hepatitis flares and hypertransaminasemia can result in high LSM level in background of low fibrosis. Therefore, the LSM level also can be used to reflect the live function (48,49).

There were several limitations in our study. The

Table 3 Univariate and multivariate analyses of the prognostic factors of RFS for HCC after RFA

Variables	Univariate			Multivariate		
	HR	95% CI	P	HR	95% CI	P
Demographic factors						
Age ≥ 55 years	1.02	0.85–1.26	0.12			
Sex (male)	0.66	0.31–1.67	0.31			
BMI ≥ 25 kg/m ²	1.03	0.99–1.12	0.24			
Liver cirrhosis	2.23	1.06–7.56	0.04	1.88	0.85–6.53	0.33
Child-Pugh stage	1.12	0.53–3.51	0.27			
MELD scores	1.56	0.88–4.66	0.06			
Tumor factors						
AFP (ng/mL)	1.00	0.98–1.01	0.21			
Tumor size (cm)	1.31	0.93–2.57	0.08			
Laboratory tests						
ALT	2.07	0.88–9.53	0.41			
ALB	0.57	0.12–2.14	0.26			
TB	2.89	1.05–8.57	0.03	2.61	1.22–8.31	0.06
PLT	1.00	0.98–1.02	0.37			
PT	1.01	0.99–1.01	0.51			
Fibrosis status						
LSM ≥ 13.4 kPa	3.12	1.08–10.25	0.02	2.87	1.03–9.15	<0.01

RFS, recurrence-free survival; HCC, hepatocellular carcinoma; CI, confidence interval; HR, hazard ratio; BMI, body mass index; AFP, alpha-fetoprotein; ALT, alanine aminotransferase; ALB, albumin; TB, total bilirubin; PLT, platelet count; PT, prothrombin time; LSM, liver stiffness measurement; MELD, model for end-stage liver disease scores.

single-center, retrospective design might influence the generalization of results, thus contributing to differences between our findings and previous study. A large multi-center prospective study would be performed to confirm the value of LSM. Moreover, in this study, we only enrolled patients with primary single HCC, not multiple or recurrent tumor, so the generalization of results was limited. Furthermore, the optimal cut-off level of LSM measurement was obtained from a patients group in a single center, which also diminished the generalizability of results. Furtherly, studies with a high evidence level may be needed to confirm the significance of LSM in prognostic evaluation of HCC.

Conclusions

In conclusion, a low LSM measured by 2D-SWE predicted a better survival in patients underwent RFA for HCC,

which also related to liver cirrhosis. Furtherly, prospective, randomized and control studies with a large scale are required to confirm the significance of LSM in HCC. The LSM by 2D-SWE, as a quantitative assessing tool for liver fibrosis, could sever as an independent prognostic predictor for HBV related HCC following RFA.

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Footnote

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure from (available at <http://dx.doi.org/10.21037/tcr.2020.03.04>). Both authors have no conflicts of interests to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Institutional Review Board of the First Affiliated Hospital of Anhui Medical University (No. C201908021).

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