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Original Article

Assessment of liver fibrosis by ultrasonic elastography and contrast enhanced ultrasonography

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Abstract: Objective: To evaluate the diagnostic performance of ultrasonic elastography combined with contrast enhanced ultrasonography in quantitative or semi-quantitative assessment of liver fibrosis. Methods: Rat Liver fibrosis model was established. According to the degree of liver fibrosis they were divided into three groups, S1 (11 cases), S2 (9 cases), S3 (7 cases) and a control group (10 cases) was established. Ultrasound elastography, contrast enhanced ultrasonography and two techniques combined method were used respectively for the diagnosis of the liver fibrosis. The diagnosis was compared with the pathological diagnosis to evaluate their clinical value. Results: HVAT and HA-HVTT were decreased with the severity of liver fibrosis (P<0.05). Semi-quantitative fibrosis scores and the relative content of collagen increased gradually with the severity of liver fibrosis. There was a significant negative correlation between HA-HVTT and semi-quantitative fibrosis scores or relative content of collagen (r_1=-0.828, r_2=-0.819) respectively. The sensitivity and specificity of the liver fibrosis diagnosis (S3) in contrast enhanced ultrasonography were 85.71% and 66.67% respectively, while they were 71.43% and 53.33% by ultrasound elastography respectively. However, the sensitivity and specificity were increased at 85.71% and 73.33% by ultrasound elastography combined with contrast enhanced ultrasonography respectively. Conclusion: Quantitative ultrasound parameters can be used as an indicator of noninvasive liver fibrosis diagnosis. Contrast enhanced ultrasonography combined with ultrasonic elastography improved the specificity and reduced the misdiagnosis rate.

Keywords: Liver fibrosis, contrast enhanced ultrasonography, ultrasonic elastograp

Introduction

Unbalanced synthesis and degradation of extracellular matrix lead to liver fibrosis [1]. Liver fibrosis is the pathological changes through cirrhosis [2]. A large number of experiments and clinical researches [3, 4] suggest that liver fibrosis can be reversed if someone gets effective treatment and without deterioration [5]. Accurate assessment and early diagnosis are directly related to the prognosis. There were usually no specific morphological changes in liver fibrosis, the traditional two-dimensional ultrasonography, which was used to reflect the anatomical structure, and the Color Doppler Flow ultrasonography, which was used to reflect the blood flow velocity, can provide only limited information. Therefore, the liver fibrosis cannot be accurately diagnosed by traditional noninvasive technique. Liver biopsy and pathological examination are the golden standards for the diagnosis of liver fibrosis [6, 7]. But they are invasive examinations, which would cause lots of complications [8, 9]. Because of the uneven distribution of liver fibrosis, diagnostic errors cannot be avoided. Moreover, liver fibrosis is a process with both damage and repair, so one liver biopsy cannot effectively reflect the whole process of liver fibrosis [10]. Thus, it has become a research hotspot to find a noninvasive diagnosis method, which is accurate, convenient, safe and economic, to evaluate liver fibrosis. It was found that by the fibrosis and cirrhosis, the liver has some changes in hardness and hemodynamics, which provides theoretical basis for ultrasonic elastography and contrast enhanced ultrosonography.

As the blood tracer, contrast agents reflect the liver blood circulation [11]. Intrahepatic cycle time of contrast agents can indirectly reveal the subtle changes of liver structure [12]. Para-

meters of contrast enhanced ultrosonography can be used in quantitative evaluation of the subtle changes in organic hemodynamics. Ultrasonic elastography is a brand new ultrasonic technique. Its basic principle relies on the application of dynamic or static/semi-static stimulation from an intrinsic (including autonomous) or extrinsic source of tissues [13, 14]. Under the physical effect of elastic mechanics and biomechanics, tissues would generate a strain as a response to relocation, reactions, and possibly a certain change in the speed, which is shown as a disturbance in distribution. Therefore, ultrasonic elastography can obtain quantitative information on distributions of elasticity in tissues.

Both ultrasonic elastography and contrast enhanced ultrosonography are new ultrasound technology. In the current study, ultrasonic elastography, contrast enhanced ultrosonography and two techniques combined methods were used to quantitate the pathological changes in the rats liver fibrosis models. The three methods were performed to find the most valuable technique for the pathological diagnosis of liver fibrosis.

Materials and methods

Experimental animals and laboratory reagents and materials

Totally 37 male or female wistar rats with weight of 200 g of clean degree were provided by the Experimental Animal Center of China Medical University. The rats were fed in the environments with the air humidity of 50-70% and the temperature of 20-29°C. 10 rats were assigned to control group, and the other 27 rats were assigned to experimental group and further divided into S1 (11 case), S2 (9 case), S3 (7 case) according to the liver fibrosis degree. All animal experiments were carried out according to the Guidelines for the Care and Use of Laboratory Animals and were approved by the Animal Experimentation Ethics Committee of China Medical University.

The main laboratory reagents and materials include SonoVue ultrasound contrast agents (Bracco Imaging, Milan, Italy), Carbon tetrachloride, Olive oil, Chloral hydrate, et al.

Ultrasonic equipment

Color ultrasonic equipment model IU22 with a linear probe and a frequency of 3-9 MHz was purchased from Philips Company (Philips, Amsterdam, Holland). Color ultrasonic equipment model HV900 with a small convex probe and a frequency of 4-8 MHz was purchased from HITACHI Company (HITACHI, Tokyo, Japan).

Establishment of liver fibrosis models

Liver fibrosis was induced by subcutaneous injection of 40% CCl_4 (Sigma-Aldrich, Darmstadt, Germany)/olive oil solution twice a week from the first to the sixth week or once a week from the seventh to the tenth week. The first dosage was 0.5 mL/100 g body weight and then each dosage was 0.3 ml/100 g body weight. Rats in the control groups received 0.5 mL of water instead of CCl_4.

Ultrasound scanning measurement

Rats were anesthetized and fixed in supine position. Upper abdomen was fully exposed and the skin was prepared. Contrast agents were injected by 0.1 ml/kg dose via the tail vein. 1.5 ml normal saline was followed. The enhancing process of liver was real-timely observed for 120 s. The images were saved into hard disk of instrument.

The images were analyzed by Qlab software (Philips, Amsterdam, Holland). The ROI area of vascular was placed in the center of vascular. Time intensity curve was drawn automatically by the computer (**Figure 1**). After the gamma regression, initial enhancement time, hepatic artery arrival time (HAAT), hepatic vein arrival time (HVAT), and time to peak (TTP) were obtained. Hepatic artery-vein transit time (HA-HVTT) and PV-parenchyma PIT (PIT) were calculated. Each rat was analyzed three times and the average value was obtained.

Calculation method: HA-HVTT = HVAT-HAAT, PIT = the parenchyma of TTP-The portal vein of TTP.

Ultrasonic elastography measurement

The rats were placed in supine position. The liver area was fully exposed. The depth and the gain were adjusted properly.

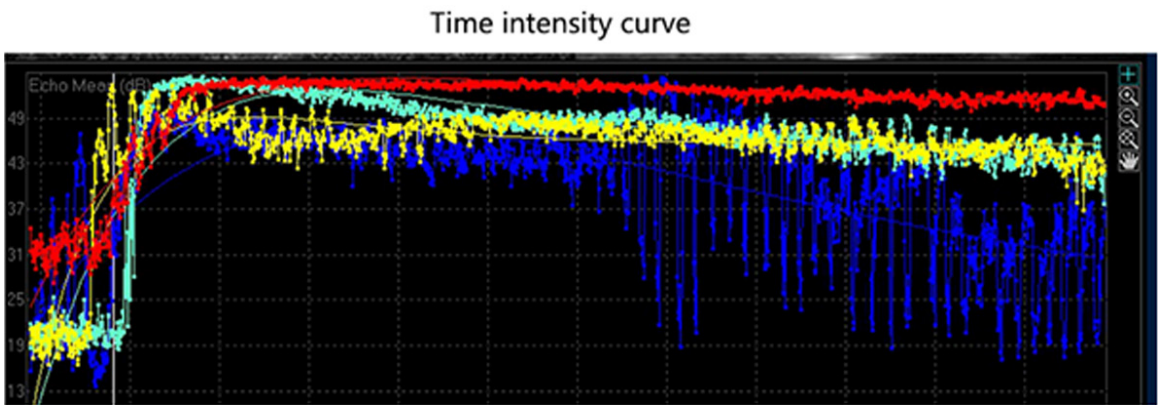

Figure 1. Time intensity curve of ultrasound scanning measurement. The red curve represents the liver parenchyma. The yellow curve represents the liver artery. The blue curve represents the liver vein. The green curve represents the portal vein.

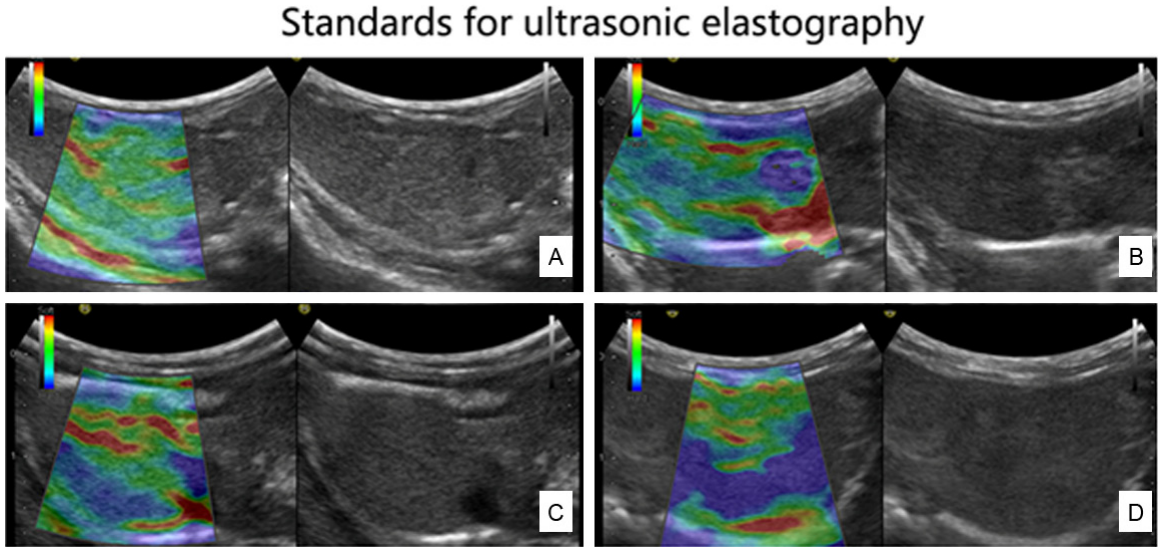

Figure 2. Evaluation standards for ultrasonic elastography. A. One score-less than 10% blue spots in the region of interest with liver membrane blue colored; B. Two scores-less than 25% blue spots in the region of interest with liver membrane blue colored; C. Three cores-less than 50% blue spots in the region of interest with liver membrane green colored; D. Four scors-more than 50% blue spots in the region of interest with liver membrane red colored.

Images were evaluated according to the following standards, one score: less than 10% blue spots in the region of interest with liver membrane blue colored; two scores: less than 25% blue spots in the region of interest with liver membrane blue colored; three scores: less than 50% blue spots in the region of interest with liver membrane green colored; four scores: more than 50% blue spots in the region of interest with liver membrane red colored (**Figure 2**). These images were evaluated by two physicians with 6-year experience.

Pathological methods

Liver tissue was embedded in 10% normal paraffin and was cut in serial sections. The slices were stained by either HE staining, Masson and reticular fiber staining.

In the 4×20 times, 5 different views in the same size were semi-quantitatively analyzed by the Nikon 90i pathological report system.

Liver fibrosis classification [15] was made according to the Scheuer classification. Liver

Table 1. The quantitative parameters of contrast enhanced ultrasonography in different stages of liver fibrosis ($\bar{x} \pm s$)

S-Stages (case)	HAAT (s)	HVAT (s)	HA-HVTT (s)	PIT (s)
Control Group (10)	9.54±0.15	11.78±0.17	2.24±0.02	2.32±0.05
S1 (11)	9.42±0.21	11.58±0.45*	2.16±0.24**	2.11±0.56
S2 (9)	9.34±0.38	10.93±0.39*	1.59±0.01**	2.31±0.31
S3 (7)	9.46±0.54	8.54±0.63*	0.92±0.09**	2.43±0.03
	F=1.145	F=22.104	F=3.893	
	P=0.346	*P*=0.017	*P*=0.000	

Note: Compared with the control group, *: *P*<0.05; Compared with the control group, **: *P*<0.01.

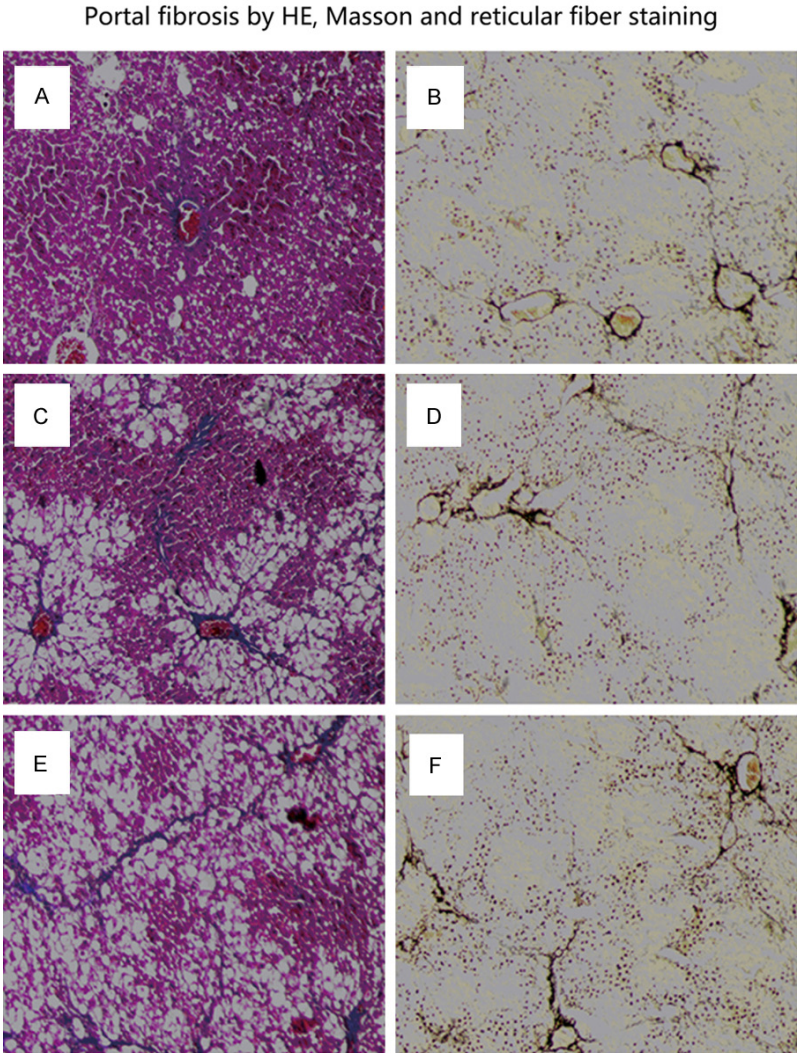

Figure 3. Portal fibrosis by HE, Masson and reticular fiber staining. A, B. Under the electron microscope (×20), Portal fibrosis without septa; C, D. Under the electron microscope (×20), Portal fibrosis with rare septa; E, F. Under the electron microscope (×20), Numerous septa without cirrhosis.

fibrosis could be divided in four stages: S1- portal fibrosis without septa; S2- portal fibrosis with rare septa; S3- numerous septa without cirrhosis; S4- cirrhosis.

Statistical analysis

Statistical analysis was performed by using SPSS 17.0 software. Quantitative data were expressed as mean ± SD. Student t test and ANOVA test were used for intergroup comparison and χ^2 test was used for counting data. The *Pearson* correlation analysis was used to analyze the relationship in variables. ROC Curve was made to measure the sensitivity and specificity of contrast enhanced ultrasonography. *P*< 0.05 was considered as statistically different.

Results

The quantitative parameters of contrast enhanced ultrasonography in different stages of liver fibrosis

There were no significant differences of HAAT and PIT between control group and experimental group (*P*> 0.05). Both HVAT and HA-HVTT decreased with the aggravation of liver fibrosis. There were significant differences in HVAT and HA-HVTT between control group and experimental group (*P*<0.05, *P*<0.01, respectively) (**Table 1**).

The relationship between HA-HVTT and the quantitation of pathological fiber in liver fibrosis

The semi-quantitative fibrosis score and the relative content of collagen increased gradually with the aggravation of liver fibrosis (**Figure 3**). From

Table 2. The comparison of HA-HVTT and the quantitative pathological fiber in liver fibrosis

S-stages (case)	HA-HVTT (s)	Semi-Quantitative Fibrosis Score	Relative Content of Collagen (%)
S1 (11)	2.16±0.24	2.04±0.86*	3.63±1.53**
S2 (9)	1.59±0.01	7.27±2.42*	11.72±3.13**
S3 (7)	0.92±0.09	10.80±1.81*	18.20±3.62**

Note: The correlation of HA-HVTT and the semi-quantitative fibrosis is r_1=-0.828, *: P<0.05, the correlation of HA-HVTT and the relative of collagen is r_2=-0.819, **: P<0.01.

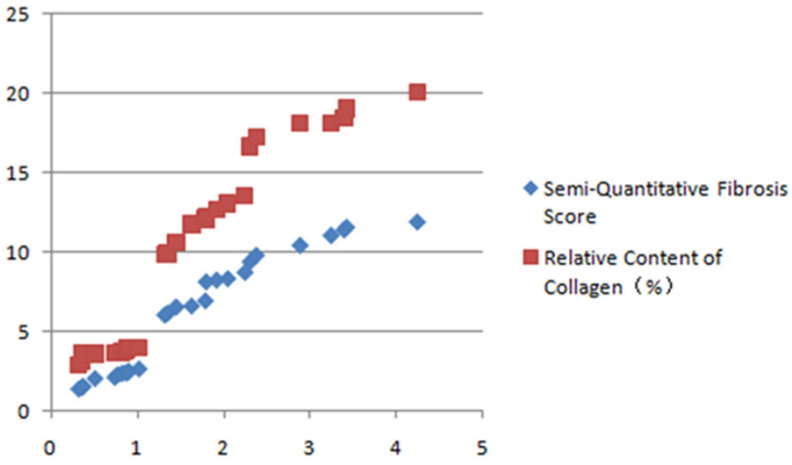

Figure 4. Scatter plot of Pearson correlation analyses on the comparison of HA-HVTT and the quantitative pathological fiber in liver fibrosis.

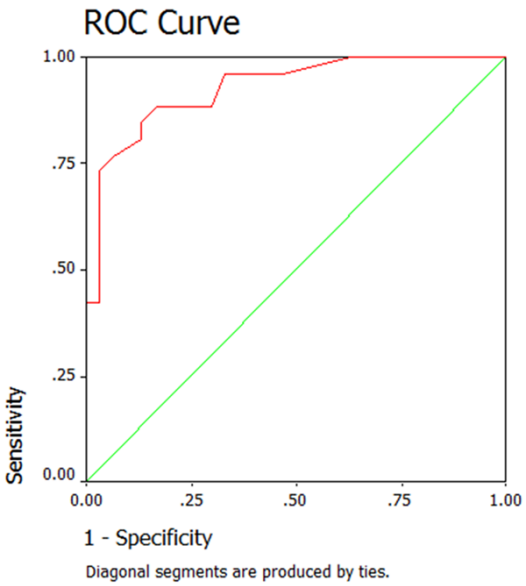

Figure 5. The ROC Curve of the quantitative parameters of contrast enhanced ultrasonography.

top to bottom, the septa in gradually increasing with the extent of the fibrosis. The correlation coefficient were r_1=-0.828, P<0.05 and r_2=-0.819, P< 0.01 respectively (**Table 2**; **Figure 4**).

The diagnostic value of HA-HVTT in liver fibrosis

The receiver operating characteristic curve (ROC Curve) of quantitative parameters of contrast enhanced ultrasonography was made. When the HA-HVTT cutoff was 0.92 s, the sensitivity and specificity of diagnosing liver fibrosis (S3) in contrast enhanced ultrasonography was 85.71% and 66.67%, respectively (**Figure 5**).

The diagnostic value of ultrasonic elastography and ultrasonic elastography combined with contrast enhanced ultrasonography in liver fibrosis

The sensitivity and specificity of diagnosis of liver fibrosis (S3) in ultrasound elastography were 71.43% and 53.33% respectively (**Table 3**).

The sensitivity and specificity of diagnosis of liver fibrosis (S3) in ultrasound elastography combined with contrast enhanced ultrasonography were 85.71% and 73.33%, respectively (**Table 4**).

The comparison of the diagnostic value of the three methods in liver fibrosis

The sensitivity of ultrasonic elastography combined with contrast enhanced ultrasonography was higher than ultrasonic elastography (P<0.01). The specificity of ultrasonic elastography combined with contrast enhanced ultrasonography was higher than ultrasonic elastography and contrast enhanced ultrasonography (P<0.01, **Table 5**).

Discussion

Researchers have long been looking for an auxiliary examination method of non-invasive imag-

Table 3. The diagnostic value of elastography in liver fibrosis

UE	Pathology		Total
	Positive S3	Negative (S0+S1+S2)	
Positive	5	14	19
Negative	2	16	18
Total	7	30	37

Note: UE (Ultrasonic Elastography).

Table 4. The diagnosis value of ultrasonic elastography combined with contrast enhanced ultrasonography in liver fibrosis

	Pathology		
UE Combined with CEUS	Positive S3	Negative (S0+S1+S2)	Total
Positive	6	8	14
Negative	1	22	23
Total	7	30	37

Note: UE (Ultrasonic Elastography); CEUS (Contrast Enhanced Ultrasonography).

Table 5. The comparison of the diagnostic value of ultrasonic elastography combined with contrast enhanced ultrasonography and respectively in liver fibrosis

	CEUS	UE	UE Combined with CEUS	
Sensitivity	85.71%	71.43%*	85.71%	*P<0.01
Specificity	66.67%*	53.33%*	73.33%	*P<0.01

Note 1: CEUS (Contrast Enhanced Ultrasonography); UE (Ultrasonic Elastography). Note 2: In comparison with the sensitivity and specificity of ultrasonic elastography combined with contrast enhanced ultrasonography respectively *: P<0.01.

ing diagnosis in liver fibrosis. Beyer D, et al. [16, 17] has reported that the diameter and spectrum of morphological changes of liver vein, the blood flow of portal vein and splenic vein could be used in grading liver fibrosis. Traditional ultrasound was one of the main the non-invasive auxiliary examination methods, which was used to assess the morphological changes of liver damages. However, it was interfered by the instruments and performers, and was short of sensitivity and specificity. It can be used to evaluate the changes of liver structure according to the two dimensional imaging, the diameter of vessel, and the parameter of Doppler ultrasound. However, it cannot be used to evaluate the early liver diffuse diseases, such as hepatitis, liver fibrosis and liver cirrhosis [18, 19].

When liver fibrosis reached a certain degree, the hepatic structure and the blood flow would change, such as hepatic artery blood flow velocity increasing, portal vein blood flow decreasing et al. [20]. As a compensatory of intrahepatic resistance, abnormal anastomosis of hepatic artery, portal vein and hepatic vein reduced liver blood transit time could be observed.

According to the time of ultrasound contrast agents appearing in organs and the change of intensity, the characteristics of the organ blood flow were analyzed [21]. As a blood tracer, ultrasound contrast agents could reflect intrahepatic blood circulation [22, 23]. Quantitative parameters by Qlab imaging analysis software could be obtained precisely. We analyzed liver fibrosis in Wistar rat models by adopting the method of transient ultrasonic elastography scores and compared it with pathological results. Our results showed that there were no significant differences of HAAT and PIT between control group and experimental group. It revealed that the hepatic artery arrival time and the TTP of portal vein to liver parenchyma were not associated with liver fibrosis. HVAT and HA-HVTT increased with liver fibrosis decreasing and a significant difference was found. This was possibly due to the abnormal anastomosis between the hepatic artery and the hepatic vein, which led to the shorter transit time of hepatic arterial and vein blood. The results showed that semi-quantitative fibrosis scores and relative content of collagen increased gradually with the aggravation of liver fibrosis grading. Semi-quantitative fibrosis scores or relative content of collagen were also negative correlated with HA-HVTT. The changes of ultrasound contrast agent circulation time in the liver suggest the fine structure of the liver. At present, the diagnosis of the diffuse liver disease with contrast enhanced ultrasonography has become the research focus in ultrasonic.

Abbattista et al. [24] proposed that if the demarcation value of diagnosing cirrhosis was HVAT less than 17 s, the sensitivity and specificity were 100% and 93.3%, respectively. Moreover, this study had a high repeatability

(Kappa =0.9). Li PC et al. [25, 26] analyzed cirrhosis quantitatively with contrast enhanced ultrasonography and proposed that ultrasound contrast agents could be used in the diagnosis of cirrhosis. Their studies showed contrast enhanced ultrasonography could not exactly distinguish liver fibrosis grading and had a low sensitivity and specificity. Our results showed that if the demarcation value of diagnosing liver fibrosis was set as HVAT =0.92 s, the sensitivity and specificity were 85.71% and 66.67%, respectively. Although other results showed that HVAT could not be used to distinguish the difference of liver fibrosis grading effectively [25, 26], most researches had reached an agreement [24, 27] that HA-HVTT could be used in the quantitative assessment of liver fibrosis. Sugimoto H et al. [27, 28] had also proposed that although there were no significant differences of HAAT and PVAT in different liver fibrosis grading, HVAT and HA-HVTT decreased gradually with the severity of liver fibrosis, which was in accordance with our results. We have also combined two techniques to diagnose liver fibrosis, and its sensitivity and specificity were 85.71% and 73.33% respectively. The combination of two techniques had improved the specificity and decreased misdiagnosis rate, which suggested that it could be used to exclude the possibility of the liver fibrosis.

In recent years, the studies on animal models and human beings found that ultrasound elastography in grading liver fibrosis were highly feasible. Sporea I et al. [29, 30] considered that FibroScan could be used to distinguish the liver fibrosis grading. Marín-Gabriel JC et al. [31] has also showed that FibroScan could be used to distinguish liver fibrosis grading, which was more accurately than Serum markers. Our results showed that the sensitivity and specificity of transient ultrasonic elastography were 87.1% and 50.0%. Although it had low specificity, it had the advantages of easy operation and shorter time-consuming. We considered that ultrasonic elastography had an important clinical value in semi-quantitative assessment of liver fibrosis grading. The sensitivity and specificity of contrast enhanced ultrasonography were higher than the ultrasonic elastography, which was similar to the results of the abovementioned researchers. Contrast enhanced ultrasonography was an important non-invasive method of grading liver fibrosis, but there were many problems in clinical application, which remained to be further improved.

Conclusion

Quantitative ultrasound parameters can be used as an indicator of noninvasive liver fibrosis diagnosis. Contrast enhanced ultrasonography combined with ultrasonic elastography improved the specificity and reduced the misdiagnosis rate.

Disclosure of conflict of interest

None.

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