

## Prospective Study

# Liver reserve function assessment by acoustic radiation force impulse imaging

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## Abstract

**AIM:** To evaluate the utility of liver reserve function by acoustic radiation force impulse (ARFI) imaging in patients with liver tumors.

**METHODS:** Seventy-six patients with liver tumors were enrolled in this study. Serum biochemical indexes, such as aminotransferase (ALT), aspartate aminotransferase (AST), serum albumin (ALB), total bilirubin (T-Bil), and other indicators were observed. Liver stiffness (LS) was measured by ARFI imaging, measurements were repeated 10 times, and the average value of the results was taken as the final LS value. Indocyanine green (ICG) retention was performed, and ICG-K and ICG-R15 were recorded. Child-Pugh (CP) scores were carried out based on patient's preoperative biochemical tests and physical condition. Correlations among CP scores,

ICG-R15, ICG-K and LS values were observed and analyzed using either the Pearson correlation coefficient or the Spearman rank correlation coefficient. Kruskal-Wallis test was used to compare LS values of CP scores, and the receiver-operator characteristic (ROC) curve was used to analyze liver reserve function assessment accuracy.

**RESULTS:** LS in the ICG-R15 10%-20% group was significantly higher than in the ICG-R15 < 10% group; and the difference was statistically significant ( $2.19 \pm 0.27$  vs  $1.59 \pm 0.32$ ,  $P < 0.01$ ). LS in the ICG-R15 > 20% group was significantly higher than in the ICG-R15 < 10% group; and the difference was statistically significant ( $2.92 \pm 0.29$  vs  $1.59 \pm 0.32$ ,  $P < 0.01$ ). The LS value in patients with CP class A was lower than in patients with CP class B ( $1.57 \pm 0.34$  vs  $1.86 \pm 0.27$ ,  $P < 0.05$ ), while the LS value in patients with CP class B was lower than in patients with CP class C ( $1.86 \pm 0.27$  vs  $2.47 \pm 0.33$ ,  $P < 0.01$ ). LS was positively correlated with ICG-R15 ( $r = 0.617$ ,  $P < 0.01$ ) and CP score ( $r = 0.772$ ,  $P < 0.01$ ). Meanwhile, LS was negatively correlated with ICG-K ( $r = -0.673$ ,  $P < 0.01$ ). AST, ALT and T-Bil were positively correlated with LS, while ALB was negatively correlated with LS ( $P < 0.05$ ). The ROC curve revealed that when the LS value was 2.34 m/s, the Youden index was at its highest point, sensitivity was 69.2% and specificity was 92.1%.

**CONCLUSION:** For patients with liver tumors, ARFI imaging is a useful tool for assessing liver reserve function.

**Key words:** Acoustic radiation force impulse; Liver reserve function; Liver tumor; Receiver-operator characteristic

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**Core tip:** Seventy-six patients with liver tumors were assessed by acoustic radiation force impulse (ARFI) imaging. We found that liver stiffness (LS) was positively correlated with Indocyanine green (ICG)-R15 and the Child-Pugh score, but was negatively correlated with ICG-K. Aspartate aminotransferase, aminotransferase and total bilirubin were positively correlated with LS, while albumin was negatively correlated with LS. The receiver-operator characteristic curve revealed that when LS value was 2.34 m/s, the Youden index was at its highest point. For patients with liver tumors, ARFI imaging is a useful tool to assess liver reserve function.

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## INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the major malignant tumors in China, and it has the third highest mortality after gastric carcinoma and lung cancer. Most HCC patients have liver fibrosis and cirrhosis<sup>[1,2]</sup>. Hepatectomy is the preferred treatment for early HCC. However, the presence of cirrhosis, results in different degrees of liver injury and low liver reserve function. Poor prognosis, such as postoperative liver failure, usually occurs<sup>[3,4]</sup>. Therefore, a good liver reserve function is a key factor for a successful surgery, and preoperative liver reserve function assessment is very important<sup>[5]</sup>. The indocyanine green (ICG) excretive test<sup>[6]</sup> and Child-Pugh (CP) scores are the main methods used to assess liver reserve function in clinical practice. However, both methods have different limitations and accuracies. In recent years, because of the development of ultrasound elastography in liver fibrosis and cirrhosis in the clinic, acoustic radiation force impulse (ARFI) imaging has become an innovative ultrasound technique that has received increasing attention<sup>[7-12]</sup>. Studies have reported<sup>[13,14]</sup> that ARFI imaging could be used for the qualitative detection of liver tumors, and that it could also be used to determine the degree of liver fibrosis by detecting liver stiffness (LS). Hence, it is hoped that this technique could evaluate liver reserve function accurately. Furthermore, ARFI imaging technology is non-invasive, simple and repeatable<sup>[15,16]</sup>. However, there have been few reports on liver reserve function assessment using ARFI imaging. Therefore, this study aimed to explore the clinical value of ARFI imaging by determining its value in assessing liver reserve function in patients with liver tumors, and providing theoretical guidance for clinical treatment.

## MATERIALS AND METHODS

### General information

Seventy-six patients with liver tumors combined with liver fibrosis or cirrhosis, who were admitted from October 2012 to May 2014, were enrolled into this study. All patients planned to receive hepatectomy. Among them, 42 patients were male and 34 patients were female. The patient age range was 33-75 years old, and the average age was  $56.71 \pm 9.32$ . Inclusion criteria: single tumor with a tumor diameter < 7 cm. There was neither intrahepatic metastasis, nor portal vein thrombosis or ascites by imaging examination. All patients were informed of the study and agreed to participate.

### Test methods

**Instruments and reagents:** Instruments: (1) Siemens ACUSON S2000™ ultrasound system<sup>[17,18]</sup>; and (2) DDG-3300K liver reserve function analyzer (Nihon Kohden, Tokyo, Japan)<sup>[19-22]</sup>. Reagent: Indocyanine green (ICG) reagent (Shenyang Jishi Pharmaceutical Co., Ltd.).

**Detection methods:** (1) Conventional serum-based liver function tests were performed including alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum albumin (ALB), total bilirubin (T-Bil) and other indicators. All data were recorded; and (2) ARFI imaging detection.

Patients underwent fasting and were kept in a left lateral position while raising the right hand. Liver right lobe tissues were detected. Patients were instructed to hold their breath. The elasticity imaging sample frame was perpendicular to the liver surface and was located 2-5 cm below the surface, avoiding nearby blood vessels. The update button was pressed to launch a high-strength low-frequency pulse. Transversal shear wave velocity (Vs, m/s) was received and recorded.

Measurements were repeated 10 times, and the average value of the Vs results was used as the LS value.

**ICG examination:** Patients were kept in a supine position. The environment was kept quiet and other factors (such as cell phones, contrast, etc.) were excluded. (1) Body weight (kg) was measured and the amount of ICG (0.5 mg/kg) was calculated; (2) an indwelling needle was injected and placed through the median cubital vein on one side to collect 2 mL of blood and determine the hemoglobin (Hb) content; (3) preparation of ICG solution, sterile water for injection/ ICG = 5 mL: 25 mg; (4) data such as Hb, weight and ICG dosage were analyzed by a DDG-3300K analyzer; (5) a sensitive probe was fixed to the patient's nose, and the entire ICG solution was injected to the median cubital vein *via* the indwelling needle in 10 s; (6) data were saved, and ICG-k and ICG-R15 were calculated; and (7) Patients were kept in a quiet environment with normal respiration at all times.

**CP score:** CP scores were carried out based on patient's preoperative biochemical tests and physical condition. CP scoring criteria are shown in Table 1.

### Research index

Biochemical index such as ALT, AST, ALB and T-Bil were observed. The correlations among CP scores, ICG-R15, ICG-K and LS values were observed and analyzed. A receiver-operator characteristic (ROC) curve was used to analyze LS indicators and assess the best diagnostic threshold of hepatic functional reserve.

### Statistical analysis

All data were analyzed using SPSS 19.0 software. Data were expressed as the mean  $\pm$  SD. To test the relationship between two variables, the Pearson correlation coefficient was used to analyze two variables if the data showed a normal distribution; while the Spearman rank correlation coefficient was used to analyze two variables if the data showed a non-normal distribution. Kruskal-Wallis test was

used to compare LS values of CP scores. LS values of non-surgical patients were expressed by sensitivity, specificity and the Youden index. A ROC curve was used to analyze liver reserve function assessment accuracy.  $P < 0.05$  means that difference was statistically significant.

## RESULTS

### Biochemical examination results

Seventy-six patients with liver tumors were successfully enrolled and assessed in this study. Serum biochemical indexes such as ALT, AST,  $\gamma$ -glutamyl transferase ( $\gamma$ -GT), ALB, T-Bil and prothrombin time (PT) are shown in Table 2.

### LS and ICG test results

The LS values of all subjects were successfully obtained. Patients with different liver reserve functions revealed different Vs values. Representative examples are shown in Figures 1 and 2. The patient in Figure 1 had a normal liver reserve function. The Vs value was 1.07 m/s, ICG-R15 was 5.13%, and ICG-K was 0.24 L/min. The patient in Figure 2 had poor liver reserve function. The Vs value was 1.75 m/s, ICG-R15 was 16.83%, and ICG-K was 0.08 L/min.

Data from all subjects revealed that the average value of ICG-R15 was  $8.13\% \pm 3.72\%$  and the ICG-K average value was  $0.24 \pm 0.29$  L/min. ICG-R15 values were divided into three groups: ICG-R15  $< 10\%$ , ICG-R15 10%-20% and ICG-R15  $> 20\%$  groups. The average LS value of the three groups is shown in Table 3. LS significantly differed among patients in the three groups ( $H = 25.89$ ,  $P = 0.000$ ). Kruskal-Wallis  $H$  test was further carried out. LS was significantly higher in the ICG-R15 10%-20% group than in the ICG-R15  $< 10\%$  group, and the difference was statistically significant ( $P < 0.01$ ). LS was significantly higher in the ICG-R15  $> 20\%$  group than in the ICG-R15  $< 10\%$  group, and the difference was statistically significant ( $P < 0.01$ ). LS was higher in the ICG-R15  $> 20\%$  group than in the ICG-R15 10%-20% group, but the difference was not statistically significant ( $P > 0.05$ ).

### CP score results

Results of different average LS, ICG-R15 and ICG-K values according to different CP scores are shown in Table 4. The average LS values were significantly different among patients with CP class A, B and C; and the difference was statistically significant ( $H = 33.84$ ,  $P = 0.0000$ ). Pairwise comparison results of LS among patients with CP class A, B and C showed that the LS value in patients with CP class A was lower than in patients with CP Class B; and the difference was statistically significant ( $P < 0.05$ ). The LS value was lower in patients with CP class A than in patients with CP Class C, while the LS value was lower in patients

**Table 1** Child-Pugh scoring criteria

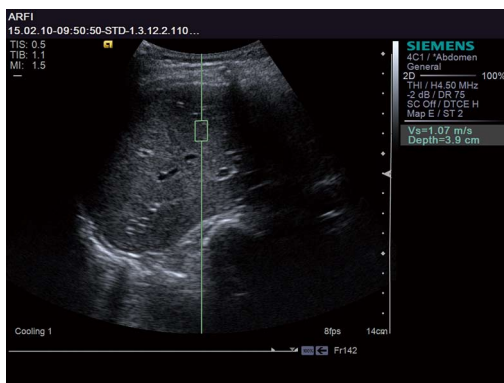
Indexes	Score		
	1 score	2 score	3 score
Hepatic encephalopathy (class)	Without	Mild	Occasional lethargy
Ascites	Without	Little/controllable by diuretics	A lot
T-Bil ( $\mu\text{mol/L}$ )	< 34	34-51	> 51
ALB (g/L)	> 35	28-35	< 28
Prolonged prothrombin time (s)	< 4	4-6	> 6

Child-Pugh class A: 5-6 score; Child-Pugh class B: 7-9 score; Child-Pugh class C:  $\geq 10$  score. T-Bil: Total bilirubin; ALB: Albumin.

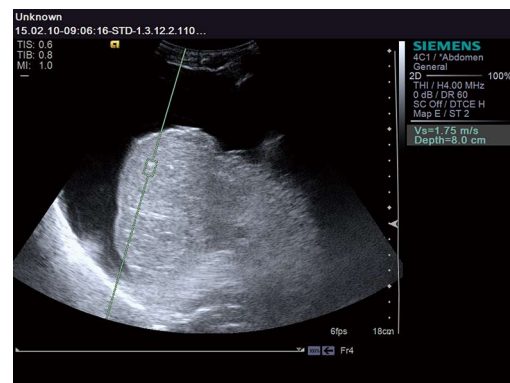
**Table 2** Biochemical examination results of patients

Indexes	mean $\pm$ SD	Media, <i>n</i>	Minimum value	Maximum value
ALT (U/L)	58.77 $\pm$ 51.13	57.81	13.74	127.28
AST (U/L)	64.21 $\pm$ 60.33	60.03	15.62	153.10
ALB (g/L)	38.19 $\pm$ 10.14	37.31	10.01	67.43
T-Bil ( $\mu\text{mol/L}$ )	26.28 $\pm$ 20.61	22.33	4.72	126.74

ALT: Aminotransferase; AST: Aspartate aminotransferase; ALB: Serum albumin; T-Bil: Total bilirubin.



**Figure 1** Patient with normal liver reserve function. The Vs value was 1.07 m/s, ICG-R15 was 5.13% and ICG-K was 0.24 L/min. ICG: Indocyanine green.



**Figure 2** Patient with poor liver reserve function. The Vs value was 1.75 m/s, ICG-R15 was 16.83% and ICG-K was 0.08 L/min. ICG: Indocyanine green.

with CP class B than in patients with CP class C; and the differences were statistically significant ( $P < 0.01$ ).

#### Correlation analysis of LS and serum biochemical tests, ICG test and CP scores

LS was positively correlated with ICG-R15 ( $r = 0.862$ ,  $P < 0.01$ ; Figure 3A) and CP scores ( $r = 0.772$ ,  $P < 0.05$ ). Meanwhile, LS was negatively correlated with ICG-K ( $r = -0.708$ ,  $P < 0.05$ ; Figure 3B). AST, ALT and T-Bil were positively correlated with LS, while ALB was negatively correlated with LS ( $P < 0.05$ ) (Table 5, Figure 3).

#### Distribution of disease in patients with liver lesions, and LS comparison between surgical and non-surgical patients

After liver reserve function assessment, 13 patients with poor liver reserve function received radiofrequency ablation (RFA) or interventional embolization, while 63 patients with normal liver reserve function received

hepatectomy. The average LS of non-surgical patients was  $2.61 \pm 0.44$  m/s, while the average LS of surgical patients was  $1.57 \pm 0.35$  m/s. The average LS of the surgical patients was lower compared with non-surgical patients, and the difference was statistically significant ( $P < 0.01$ ). The ROC curve is shown in Figure 4. When the LS value was 2.34 m/s, the Youden index was at its highest point, sensitivity was 69.2% and specificity was 92.1%.

## DISCUSSION

Liver reserve function assessment is receiving increasingly attention from hepatobiliary surgeons. Preoperative evaluation of liver reserve function is very important for selecting a reasonable surgical method and a reasonable liver resection range, leading to a successful surgery and preventing postoperative hepatic failure<sup>[23]</sup>. CP scores are the main methods used to assess liver reserve function

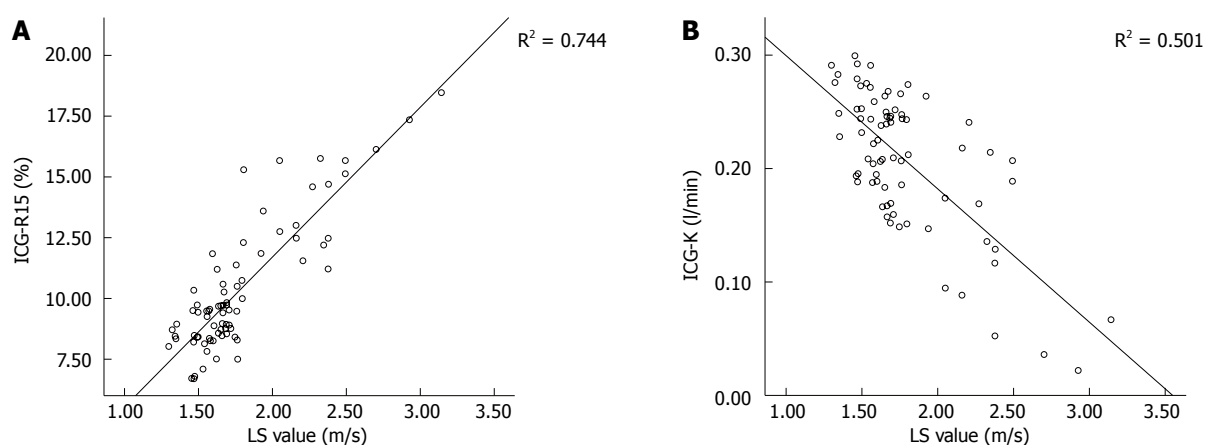


**Table 3** Average values of liver stiffness, indocyanine green-R15 and indocyanine green-K in each group, based on indocyanine green-R15 grouping

Groups	Number of cases	LS average value (m/s)	ICG-R15 (%)	ICG-K (L/min)
< 10%	57	1.59 ± 0.32	8.99 ± 2.15	0.19 ± 0.04
10%-20%	16	2.19 ± 0.27 <sup>a</sup>	13.54 ± 2.12	0.16 ± 0.05
> 20%	3	2.53 ± 0.29 <sup>a</sup>	17.32 ± 0.73	0.11 ± 0.07

<sup>a</sup>*P* < 0.05, *vs* the < 10% group. LS: Liver stiffness; ICG: Indocyanine green.**Table 4** Different average liver stiffness, indocyanine green-R15 and indocyanine green-K values according to different Child-Pugh scores

CP class	Cases	LS average value (m/s)	ICG-R15 (%)	ICG-K (L/min)
Class A (5-6)	48	1.57 ± 0.34	8.90 ± 3.67	0.23 ± 0.04
Class B (7-9)	15	1.86 ± 0.27 <sup>a</sup>	11.38 ± 2.71	0.19 ± 0.05
Class C (10-15)	13	2.47 ± 0.33 <sup>a,c</sup>	14.44 ± 3.58	0.14 ± 0.07

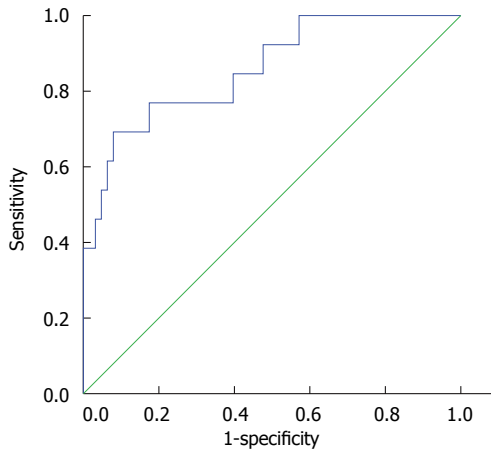
<sup>a</sup>*P* < 0.05, *vs* class A; <sup>c</sup>*P* < 0.05, *vs* the class B. CP: Child-Pugh; LS: Liver stiffness; ICG: Indocyanine green.**Figure 3** Correlations between liver stiffness and indocyanine green-R15 (A) or indocyanine green-K (B) levels are shown. LS: Liver stiffness.

in clinical practice<sup>[24,25]</sup>, and ICG excretion tests have become an important reference for surgical decision making<sup>[26]</sup>. The ICG test has been widely used to determine liver reserve function, which is an important indicator to assess surgical safety. However, ICG tests need to be excreted through the biliary tract, which is not suitable for patients with obstructive jaundice. Hence, its application is restricted. The ARFI imaging technology applied in this study is not restricted. ARFI imaging is non-invasive, simple and repeatable, and has more extensive applications. Therefore, this study evaluated the clinical value of ARFI imaging to assess liver reserve function in patients with liver tumors, providing theoretical guidance for clinical treatment.

#### Correlation analysis between LS and liver reserve function index

As liver fibrosis develops, LS increases, while liver compliance and elasticity decrease<sup>[27]</sup>. Lupsor *et al.*<sup>[28]</sup> reported that there was a significant correlation between LS value and liver fibrosis stage. This proved

that ARFI imaging could also be used to determine the degree of liver fibrosis by detecting LS, and to correctly evaluate liver reserve function. In this study, there was a strong positive correlation between LS and ICG-R15, and a negative correlation between LS and ICG-K. ICG-R15 values were divided into three groups: ICG-R15 < 10%, ICG-R15 10%-20% and ICG-R15 > 20% groups. LS significantly differed among patients in the three groups. LS was significantly higher in the ICG-R15 10%-20% group compared with the ICG-R15 < 10% and ICG-R15 > 20% groups. LS was significantly higher in the ICG-R15 > 20% group than in the ICG-R15 < 10% group. LS was higher in the ICG-R15 > 20% group than in the ICG-R15 10%-20% group, but there was no statistical significance. This implied that the LS value increases as ICG-R15 levels increase, resulting in reduced hepatic clearance and aggravated liver damage. This also demonstrated that ARFI imaging could be used to determine the degree of liver fibrosis by detecting LS, and to evaluate liver reserve function.



**Figure 4** Receiver-operator characteristic curve used to analyze liver reserve function assessment accuracy. When the liver stiffness value was 2.34 m/s, the Youden index was at its highest point, sensitivity was 69.2% and specificity was 92.1%.

#### Correlation between LS values and CP scores

CP scores can reflect liver cell damage. The higher the score, the more severe the hepatic dysfunction. In this study, LS values for CP class A, B and C were  $1.57 \pm 0.34$  m/s,  $1.86 \pm 0.27$  m/s and  $2.47 \pm 0.33$  m/s, respectively. Comparative results of LS values among the three CP classes revealed that: the LS value of CP class A was lower than CP class B, and the LS value of class A and B were significantly lower than CP class C. These results showed that LS values increase as CP scores increase. This outcome reflected severe liver function damage, causing LS values to increase, while the liver reserve function decreases. Therefore, this also demonstrated that LS values could reflect liver reserve function. CP scores could be used to evaluate liver reserve function based on routine liver function tests. CP scores are widely used in clinical practice because they are an easy method of detection. However, traditional biochemical indicators simply reflect the degree of liver cell damage and compensation function status; and the reserve capacity of the liver could not be accurately predicted when the body is exposed to trauma, infection, surgery and other invasions<sup>[29]</sup>. Therefore, ARFI imaging technology can supplement the CP scoring method; providing a more detailed liver reserve function assessment for predicting body endurance and permits a better choice of treatment modes.

#### Best diagnostic threshold of liver reserve function as assessed by LS indicators

Average LS values were lower in surgical patients compared with non-surgical patients. The ROC curve revealed that when the LS value was 2.34 m/s, the Youden index was at its highest point, sensitivity was 69.2% and specificity was 92.1%; which demonstrated that the higher the LS value, the worse the liver reserve function and prognosis after surgery. This also confirmed that LS values could react to liver reserve

**Table 5** Correlations between liver stiffness and liver function index

Index	<i>r</i>	<i>P</i> value
ICG-R15	0.862	0.000
ICG-K	-0.708	0.000
CP score	0.772	0.000
AST	0.318	0.024
ALT	0.493	0.001
ALB	-0.511	0.001
T-Bil	0.225	0.017

ICG: Indocyanine green; CP: Child-Pugh; ALT: Aminotransferase; AST: Aspartate aminotransferase; ALB: Serum albumin; T-Bil: Total bilirubin.

functions. Furthermore, an LS value greater than 2.34 m/s suggested poor liver reserve function; therefore, non-surgical treatment is recommended. Clinicians can use ARFI imaging technology to measure LS value and assess liver reserve function to determine if a patient is suitable for surgery; thereby, providing a more suitable treatment option for patients.

#### Limitations and prospects

Although ARFI imaging is expected to provide fast, simple and accurate guidance in assessing liver reserve function in clinical practice, there are also limitations for the use of ARFI imaging. We found that ARFI imaging has high requirements from the patient. It requires patients to keep holding their breath during the course of the examination, which is difficult for elderly patients or patients in poor physical condition. The ARFI sampling frame would show deviations caused by a patient's breathing problems, which would affect the accuracy of the measurement. To compensate for this limitation, we repeated the measurement 10 times to reduce errors. In addition, there were few subjects in this study. Seventy-six cases are not sufficient to demonstrate that  $LS > 2.34$  m/s is the best demarcation point. Large multicenter studies are needed to obtain enough data for analysis and to provide convincing evidence.

In conclusion, ARFI could be used to determine liver reserve function by detecting LS. ARFI imaging has advantages, such as speed, simplicity, and non-invasiveness, and has a wide range of applications. It is important to determine a reasonable surgical method and liver resection range. ARFI imaging technology is a useful tool to assess liver reserve function in patients with liver tumors. It has an important clinical application and should be promoted.

## COMMENTS

#### Background

Hepatocellular carcinoma (HCC) is one of the major malignant tumors in China. It has the third highest mortality after gastric carcinoma and lung cancer. Most patients with HCC have liver fibrosis and cirrhosis. Hepatectomy is the preferred treatment for early HCC. However, most HCC patients also have chronic liver diseases, such as cirrhosis, resulting in different degrees of liver

injury and low liver reserve function. Poor prognosis, such as postoperative liver failure, usually occurs. Therefore, a good liver reserve function is a key factor for a successful operation, and preoperative liver reserve function assessment is of great importance.

### Research frontiers

In recent years, because of the development of ultrasound elastography in liver fibrosis and cirrhosis in clinic, acoustic radiation force impulse (ARFI) imaging has become an innovative ultrasound elastography that has received increasing attention. Studies have reported that ARFI imaging could be used for the qualitative detection of liver tumors, and could also be used to determine the degree of liver fibrosis by detecting liver stiffness (LS). Hence, it is hoped that this technique could evaluate liver reserve function accurately. Furthermore, ARFI imaging is non-invasive, simple and repeatable.

### Innovations and breakthroughs

ARFI could be used to determine liver reserve function by detecting LS. ARFI imaging has advantages, such as speed, simplicity, non-invasiveness, and a wide range of applications. It is important to determine a reasonable surgical method and liver resection range. ARFI imaging technology is a useful tool to assess liver reserve function in patients with liver tumors. It has an important clinical application and should be promoted.

### Applications

This study demonstrated that ARFI imaging could be used to assess liver reserve function by detecting LS, and to determine a more successful surgical option. The results showed that the higher the LS value, the worse the liver reserve function and prognosis after surgery. This also confirmed that LS values could react to liver reserve functions. Furthermore, an LS value greater than 2.34 m/s suggested poor liver reserve function; therefore, non-surgical treatment should be recommended.

### Peer-review

This study demonstrated that ARFI imaging could be used to assess liver reserve function by detecting LS before surgery. This provides a means of determining a reasonable surgical method for patients with liver tumors. ARFI imaging has advantages. It is fast, simple, non-invasive and has a wide range of applications. Thus, ARFI imaging is a useful and valuable tool for clinical application and should be promoted.

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