World Journal of Gastroenterology

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DOI: 10.3748/wjg.v22.i22.5276

World J Gastroenterol 2016 June 14; 22(22): 5276-5284
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

ORIGINAL ARTICLE

Observational Study

Primary biliary cirrhosis degree assessment by acoustic radiation force impulse imaging and hepatic fibrosis indicators

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Institutional review board statement: The study was reviewed and approved by the Huashan Hospital Baoshan Branch Affiliated to Fudan University Institutional Review Board.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: We declare that there are no conflicts of interest to disclose.

Data sharing statement: No additional data are available.

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Received: January 24, 2016
Peer-review started: January 25, 2016
First decision: February 18, 2016
Revised: March 2, 2016
Accepted: March 30, 2016
Article in press: March 30, 2016
Published online: June 14, 2016

Abstract

AIM: To evaluate the assessment of primary biliary cirrhosis degree by acoustic radiation force impulse imaging (ARFI) and hepatic fibrosis indicators.

METHODS: One hundred and twenty patients who developed liver cirrhosis secondary to primary biliary cirrhosis were selected as the observation group, with the degree of patient liver cirrhosis graded by Child-Pugh (CP) score. Sixty healthy individuals were selected as the control group. The four indicators of hepatic fibrosis were detected in all research objects, including hyaluronic acid (HA), laminin (LN), type Ⅲ collagen (PC Ⅲ), and type Ⅳ collagen (Ⅳ-C). The liver parenchyma hardness value (LS) was then measured by ARFI technique. LS and the four indicators of liver fibrosis (HA, LN, PC Ⅲ, and Ⅳ-C) were observed in different grade CP scores. The diagnostic value of LS and the four indicators of liver fibrosis in determining liver cirrhosis degree with PBC, whether used alone or in combination, were analyzed by receiver operating characteristic (ROC) curve.

RESULTS: LS and the four indicators of liver fibrosis within the three classes (A, B, and C) of CP scores in the observation group were higher than in the control

group, with C class > B class > A class; the differences were statistically significant (P < 0.01). Although AUC values of LS within the three classes of CP scores were higher than in the four indicators of liver fibrosis, sensitivity and specificity were unstable. The ROC curves of LS combined with the four indicators of liver fibrosis revealed that: AUC and sensitivity in all indicators combined in the A class of CP score were higher than in LS alone, albeit with slightly decreased specificity; AUC and specificity in all indicators combined in the B class of CP score were higher than in LS alone, with unchanged sensitivity; AUC values (0.967), sensitivity (97.4%), and specificity (90%) of all indicators combined in the C class of CP score were higher than in LS alone (0.936, 92.1%, 83.3%).

CONCLUSION: The diagnostic value of PBC cirrhosis degree in liver cirrhosis degree assessment by ARFI combined with the four indicators of serum liver fibrosis is of satisfactory effectiveness and has important clinical application value.

Key words: Acoustic radiation force imaging technology; Hepatic fibrosis index; Primary biliary cirrhosis; Diagnostic value

Core tip: One hundred and twenty patients who had developed liver cirrhosis from primary biliary cirrhosis were assessed by ARFI imaging and hepatic fibrosis index alongside sixty healthy individuals. The ROC curves of LS combined with four liver fibrosis indexes showed that the AUC values (0.967), sensitivity (97.4%), and specificity (90%) of all indexes combined in the C grade of CP score were higher than in those of LS alone (0.936, 92.1%, and 83.3%). The diagnostic value of PBC cirrhosis degree in liver cirrhosis degree assessment by ARFI combined with the four indicators of serum liver fibrosis is of satisfactory effectiveness and has important clinical application value.

Zhang HC, Hu RF, Zhu T, Tong L, Zhang QQ. Primary biliary cirrhosis degree assessment by acoustic radiation force impulse imaging and hepatic fibrosis indicators. *World J Gastroenterol* 2016; 22(22): 5276-5284 Available from: URL: http://www.wjgnet.com/1007-9327/full/v22/i22/5276.htm DOI: http://dx.doi.org/10.3748/wjg.v22.i22.5276

INTRODUCTION

Primary biliary cirrhosis (PBC) is a chronic cholestatic disease[1] that can develop into liver fibrosis, cirrhosis[2-4], and even lead to liver failure[5]. When a patient is already in the liver cirrhosis stage, accurate diagnosis, and assessment of the extent of liver cirrhosis is vital to the diagnosis, treatment, and prognosis of the disease[6]. Therefore, exploring a high value examination method to diagnose liver cirrhosis is very significant[7-9]. It has been reported that liver cirrhosis can be divided into three classes according to the Child-Pugh (CP) scoring criteria, and the accuracy of their assessment methods have been demonstrated[10-13]. Although liver biopsy is still currently the preferred diagnostic method for cirrhosis, the resulting trauma to the patient's body leads to low acceptance[14-17]. Serum fibrosis indicators are a non-invasive examination method of cirrhosis diagnosis with a wide range of applications[18], however its accuracy in the assessment of cirrhosis degree remains to be studied[19]. Acoustic radiation force impulse imaging (ARFI) is a new ultrasound elastography technique[20] that can detect the hardness of the liver parenchyma for liver disease accurate assessment, and is non-invasive, simple, repeatable[21-23], and it can effectively compensate for the lack of liver biopsy and serum liver fibrosis markers. ARFI technology in China remains at the clinical development phase[24-26]. However, comparative studies of ARFI technology and other methods to assess the degree of liver cirrhosis and joint applications are few[27-30]. This study intends to use the CP score as a grading standard, as well as to observe the comparison of ARFI technology measured serum fibrosis markers alone and in combination with diagnostic accuracy to find a more satisfactory diagnostic method for PBC, with the aim of providing a theoretical basis for the clinical diagnosis and treatment of liver cirrhosis.

MATERIALS AND METHODS

General information

From January 2014 to September 2015, 120 patients with primary cholestatic cirrhosis that had developed to the stage of cirrhosis and were admitted to Huashan Hospital (Baoshan Branch Affiliated to Fudan University, Shanghai, China) were selected as the observation group. The patients consisted of 35 males and 85 females, with an average age of 56.33 ± 7.42 years. Patients were divided into different groups according to Child-Pugh score as follows: grade A, 39 cases; grade B, 43 cases; and grade C, 38 cases. Meanwhile, 60 healthy subjects were chosen as the control group, and consisted of 24 males and 36 females, with an average age of 54.27 ± 8.31 years. General information on the differences between these two groups was not statistically significant (P > 0.05). This study was approved by the ethics committee.

Diagnostic criteria

The degree of liver cirrhosis in patients was diagnosed based on symptoms, signs, CT, MRI, biochemical examination, and liver biopsy results.

Table 1 Child-Pugh scoring criteria

Indicator	Score		
	1 point	2 point	3 point
Hepatic encephalopathy (grade)	None	Slight	Occasional drowsiness
Ascites	None	Small amount of diuretics can be controlled	Numerous
Total bilirubin (μmol/L)	< 34	34-51	> 51
Albumin (g/L)	> 35	28-35	< 28
Prolonged prothrombin time(s)	< 4	4-6	> 6

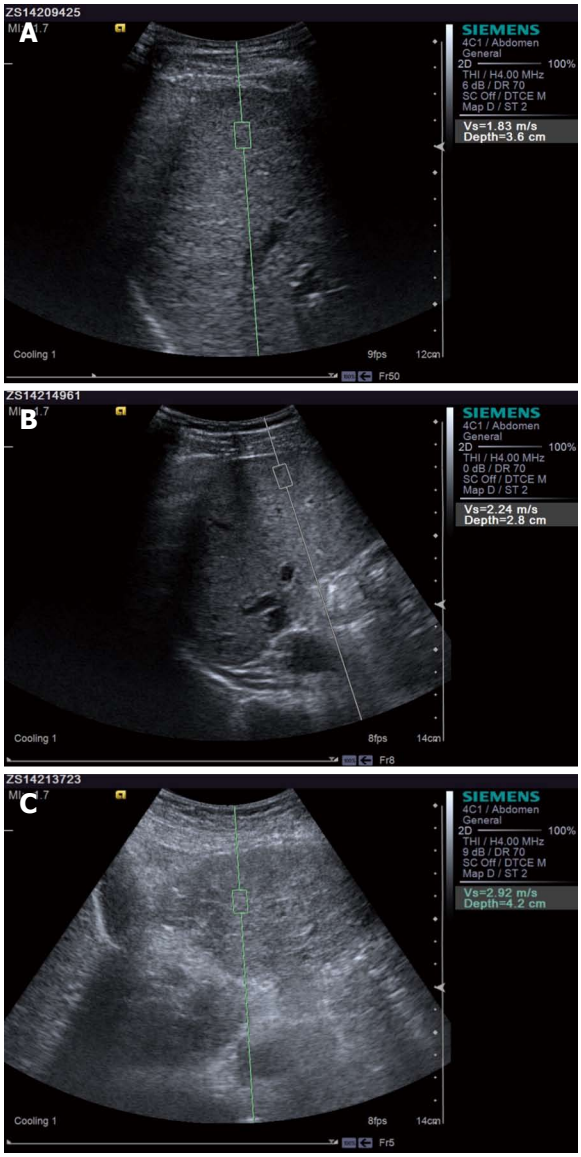

Figure 1 Observation group CP scores in the three classes. A: CP score patients with cirrhosis (Vs = 1.83 m/s); B: CP score patients with cirrhosis (Vs = 2.24 m/s); C: CP score patients with cirrhosis (Vs = 2.92 m/s).

Inclusion criteria

(1) Diagnosed with PBC that has developed to liver cirrhosis; (2) healthy subjects with no hepatobiliary diseases; (3) independent and able to cooperate with the test; and (4) provided written informed consent.

Exclusion criteria

(1) Patients with liver cancer or heart, lung, or other vital organs diseases; (2) disturbance of consciousness or mental illness; and (3) patients who provided written informed consent, but failed to cooperate with the test.

Child-Pugh scoring criteria

Patients were scored according to hepatic encephalopathy, peritoneal effusion, total bilirubin and albumin content, prolonged prothrombin time, and other conditions. Child-Pugh classification criteria (Table 1): class A, 5-6 points; class B, 7-9 points; and class C, ≥ 10 points.

Research methods

Liver fibrosis index detection: (1) After fasting, 5 ml of morning blood samples were collected from patients and kept at room temperature for approximately 30 min; (2) serum was separated and stored at -70 ℃; and (3) four indexes of liver fibrosis were determined using fluorescence immunoassay: hyaluronic acid (HA), laminin (LN), procollagen Ⅲ (PC Ⅲ), and collagen Ⅳ (Ⅳ-C).

ARFI detection: Siemens ACUSON S2000 color ultrasound diagnostic apparatus was used to conduct ARFI detection. (1) After fasting, the patient was placed on the left lateral position with the right hand on the head, and the right lobe of the liver tissue was detected; (2) elastic sampling frame was perpendicular to the surface of the liver, with a depth of approximately 2-5 cm while avoiding the surrounding blood vessels, and the patient was asked to hold their breath; and (3) the update button was pressed, a high-strength low-frequency pulse was launched, and the transverse shear wave velocity (Vs) was received. Units were in m/s and the value was recorded. Measurements were repeated 10 times and Vs were averaged to determine liver parenchyma hardness LS value.

Statistical analysis

SPSS 17.0 statistical software was used for all data results. LS value and the four indicators of liver fibrosis were measurement data presented as mean ± SD, with groups compared using two independent samples *t*-test. To evaluate the diagnostic value of LS value and the four serum indicators for liver fibrosis detected by ARFI (HA, LN, PCⅢ, and Ⅳ-C) for PBC, receiver operating characteristic (ROC) curve analysis with the area under the ROC curve (AUC), sensitivity and specificity representations were used. $P < 0.05$ was

Table 2 Test results of two groups of indicators (mean ± SD)

Item	Control group (n = 60)	Observation group		
		A class (n = 39)	B class (n = 43)	C class (n = 38)
LS value (m/s)	1.03 ± 0.03	1.90 ± 0.07[a]	2.31 ± 0.02[a]	2.92 ± 0.17[a]
HA (ng/mL)	54.96 ± 21.13	431.01 ± 118.04[a]	619.03 ± 164.28[a]	857.13 ± 192.05[a]
LN (ng/mL)	79.11 ± 15.37	116.14 ± 18.77[a]	153.42 ± 36.25[a]	211.09 ± 30.18[a]
PCⅢ (ng/mL)	89.91 ± 18.76	142.51 ± 30.07[a]	227.93 ± 69.11[a]	367.39 ± 99.21[a]
Ⅳ-C (ng/mL)	51.32 ± 9.27	104.58 ± 42.17[a]	168.99 ± 32.14[a]	193.36 ± 30.22[a]

[a]P < 0.01 *vs* the control group.

Table 3 Receiver operating characteristic curves results of different CP score classifications of liver cirrhosis with different indicators of diagnosis

Item	A Class			B Class			C Class		
	AUC	Sensitivity	Specificity	AUC	Sensitivity	Specificity	AUC	Sensitivity	Specificity
LS value	0.852	57.9%	93.3%	0.911	97.4%	75.0%	0.936	92.1%	83.3%
HA	0.694	97.4%	55.0%	0.852	97.4%	65.0%	0.888	63.2%	96.7%
LN	0.707	97.4%	43.3%	0.746	46.2%	96.7%	0.828	97.4%	58.3%
PCIII	0.741	57.9%	86.7%	0.823	53.8%	96.7%	0.871	86.8%	75.0%
IV-C	0.688	78.9%	56.7%	0.785	97.4%	51.7%	0.889	94.7%	73.3%

considered statistically significant.

RESULTS

Test result indicators in the two groups

CP scores, LS values, and the four serum indicators for liver fibrosis in the three classes (A, B, and C) of patients in the observation group were significantly higher than controls; the difference was statistically significant (P < 0.01). In the observation group, CP scores in the three classes of patients, LS values (Figure 1), and the four serum indicators for liver fibrosis revealed that class C > class B > class A; differences were statistically significant (P < 0.01), as shown in Table 2.

ROC curve analysis of LS value and the four indicators of serum liver fibrosis in the observation group

ROC curve analysis of LS values and the four diagnostic indicators of liver fibrosis of CP rates in different cirrhosis grades and each index of the AUC showed: grade C > grade B > grade A, as well as that the sensitivity and specificity were different (Table 3). Comparison of results of CP levels of LS values and the four indicators of liver fibrosis in the ROC curve are as follows:

In CP score grade A, LS values in the AUC and the specificity were high compared with serum liver fibrosis, albeit with lower sensitivity (Figure 2A).

In grade B, the AUC value of LS and specificity were high compared with HA and Ⅳ-C, but with lower sensitivity; AUC and sensitivity were high compared with LN and PCⅢ, but with lower specificity (Figure 2B).

In grade C, AUC values of LS, sensitivity, and specificity were high compared with PCⅢ; AUC and sensitivity were high compared with HA, but with lower specificity; AUC and specificity were high compared with LN and Ⅳ-C, but with lower sensitivity (Figure 2C).

ROC curve analysis of LS value in the observation group combined with the four indicators of serum liver fibrosis

LS values detected by ARFI in the observation group combined with the four indicators of serum liver fibrosis in the ROC curve show the following (Table 4): in each indicator of CP score grade A, the AUC and sensitivity were higher than the LS value detected by ARFI alone, although its specificity decreased slightly (Figure 3A); in CP score grade B, the AUC and sensitivity were higher than LS detected by ARFI alone, with sensitivity being constant (Figure 3B); in CP score grade C, the AUC, sensitivity, and specificity were higher than the LS values detected by ARFI alone (Figure 3C).

DISCUSSION

Cholestatic liver cirrhosis is a chronic liver disease with a long and gradual progression to liver cirrhosis[31-34]. An accurate assessment of early liver cirrhosis can effectively prevent further liver damage that can result in liver failure[35-37]; this has great significance for the diagnosis, treatment, and prognosis of chronic liver disease[38-40]. In this study, by comparing the diagnostic values of AFRI detected LS values and the four indicators (HA, LN, PCⅢ, and Ⅳ-C) of serum liver fibrosis alone or in combination, we aimed to accurately and effectively explore this examination

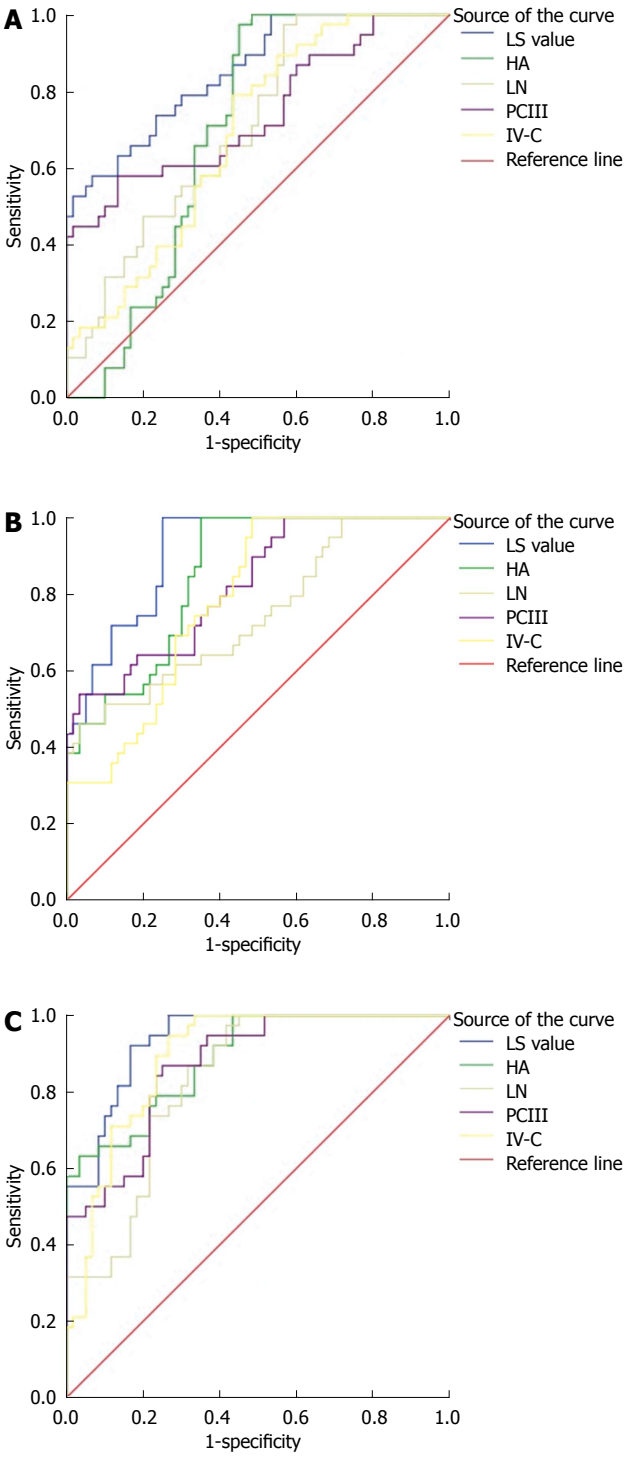

Figure 2 Comparison of the results of CP levels of LS values and the four indicators of liver fibrosis in the ROC curve. A: CP score for each indicator; B: CP score of the various indicators; C: CP score of the various indicators.

method for the assessment of cirrhosis degree.

LS values and the four indicators of serum liver fibrosis in observation and control groups

Liver stiffness increases as chronic liver disease develops to liver fibrosis and cirrhosis. In this study, the LS value results and four indicators of serum liver fibrosis in the observation group showed class C > class B > class A trends; the level of indicators were significantly higher. LS values and the four indicators of serum liver fibrosis of cirrhotic patients were higher than in the control group; this increased as liver cirrhosis degree increased. This also proves that ARFI-detected LS values and the four indicators of serum liver fibrosis can reflect changes in the degree of cirrhosis. Studies have reported[41] that AFRI-detected LS values increased as the degree of hepatic fibrosis increased; this can be widely used in patients with chronic liver disease. In recent years, this research has garnered more attention. The four serum fibrosis indicators for liver damage can be assessed via changes in each indicator, and thus can effectively diagnose cirrhosis. However, its detection accuracy for liver cirrhosis degree remains as yet unconfirmed[42].

Table 4 Receiver operating characteristic curve analysis for LS values combined with the four indicators of serum liver fibrosis

	LS value			Combination		
	AUC	Sensitivity	Specificity	AUC	Sensitivity	Specificity
A Class	0.852	57.9%	93.3%	0.881	68.4%	91.7%
B Class	0.911	97.4%	75.0%	0.973	97.4%	85.0%
C Class	0.936	92.1%	83.3%	0.967	97.4%	90.0%

ROC curve analysis of LS values and the four indicators of liver fibrosis

In the ROC curve analysis of LS value and the four indicators of liver fibrosis, we found the following: LS value and the four indicators of liver fibrosis in the AUC are present in class C > class B > class A trends, and that the diagnostic accuracy of each indicator can increase with increased liver cirrhosis degree (*i.e.*, each indicator can assess the degree of cirrhosis). While each indicator for the diagnostic value of different grades of liver cirrhosis are different, a comparison of results from the ROC curves show that the CP score of the three classes in the AUC were higher than in the four indicators of liver fibrosis, but that its sensitivity and specificity were unstable. CP score class A: LS values were higher than that of serum-specific liver fibrosis, but with lower sensitivity; CP score class B: LS values and specificity were higher than HA and Ⅳ-C, but with lower sensitivity (sensitivity was higher than LN and PCⅢ, but with lower specificity); CP score class C: LS values and sensitivity were higher than HA, but with lower specificity (specifically was higher than LN and Ⅳ-C, but with relatively lower sensitivity). The results show that the diagnostic value of LS values is high compared to the four indicators of liver fibrosis and that it has high diagnostic accuracy, although its diagnostic sensitivity and specificity is unstable. The sensitivity of the four indicators of liver fibrosis for the diagnosis of cirrhosis degree is strong, but its

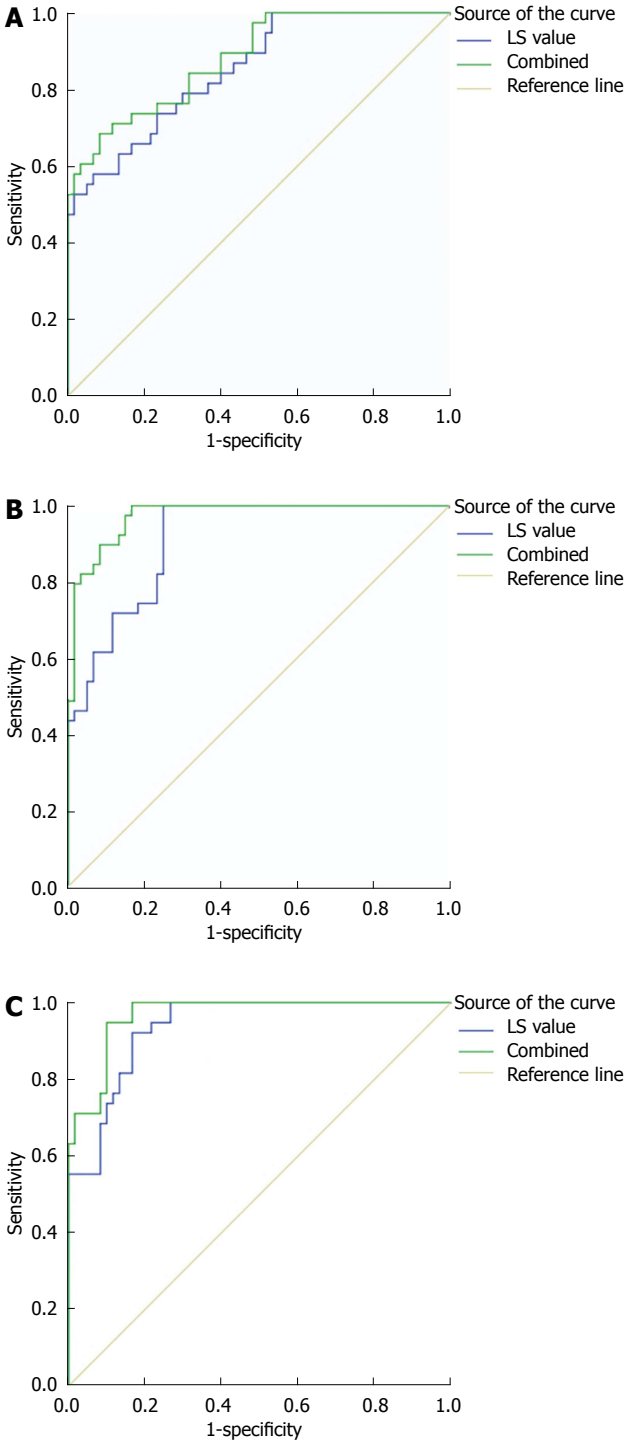

Figure 3 Receiver operating characteristic curve analysis for LS values combined with the four indicators of serum liver fibrosis. A: CP score of all indicators combined; B: CP score of all indicators combined; C: CP score of all indicators combined.

specificity and overall diagnostic value are insufficient. Detection of the four indicators of serum liver fibrosis can effectively diagnose cirrhosis, but lacks specificity in the accurate assessment of cirrhosis degree; thus, its technical support requires improvement[43]. The most commonly used method for the clinical diagnosis of cirrhosis is liver biopsy. However, due to its invasiveness, it has low acceptance limitations and causes more distress in clinical diagnosis and treatment to a certain extent[44-46]. On the other hand, ARFI ultrasound is a non-invasive detection technology. The degree of liver fibrosis can be determined by detecting LS value, which can compensate for the weakness of liver biopsy in detecting liver fibrosis[47].

ROC curve analysis of LS value combined with the four indicators of liver fibrosis

In the observation group, the results of the ROC curve analysis of LS value combined with the four indicators of serum liver fibrosis revealed that the CP score of the three classes combined with the diagnosis of AUC values were higher than ARFI-detected LS values alone, with sensitivity and specificity also improving. CP score class A: combined diagnosis sensitivity was higher than the LS value, albeit with slightly decreased specificity; CP score class B: the combined diagnostic specificity value was higher than the LS value, but sensitivity remained unchanged and there was no reduction; CP score class C: combined diagnostic sensitivity and specificity values were higher than the LS value. These results show that combined diagnosis improves the diagnostic accuracy of single-use LS values, and that diagnostic sensitivity and specificity can be guaranteed. The combined diagnostic value of LS values is high compared to the four indicators of liver fibrosis. It also proves that the LS value combined with the four indicators of serum liver fibrosis in the diagnosis of cirrhosis degree is higher than the diagnostic value of each indicator alone.

Limitation and prospects

Requirements for AFRI examination in patients were stringent. This may be due to insufficient coordination between doctors and patients, which affects the accuracy of the examination[48-50]. The detection operation for the four indicators of serum liver fibrosis is relatively simple, but also has its own shortcomings. Combined diagnosis can therefore play a complementary role and help improve diagnostic accuracy. Furthermore, LS values and indicators of liver fibrosis by way of motion detection can assist doctors in understanding the condition of a patient's liver disease, which is of great significance in the diagnosis and prognosis of liver cirrhosis.

In summary, the clinical diagnostic value of AFRI-detected LS value for determining liver cirrhosis degree is high compared to the four indicators of serum liver fibrosis. The diagnostic value of two combined diagnostics was more satisfactory compared to the indicators alone. Thus, detection by AFRI technology combined with the four indicators of serum liver fibrosis may serve as a powerful tool for determining liver cirrhosis degree, which has important clinical value and is worthy of wide promotion.

COMMENTS

Background

Primary biliary cirrhosis (PBC) is a chronic cholestatic disease that may develop into liver fibrosis, cirrhosis, and even lead to liver failure. When the patient is already in the liver cirrhosis stage, the accurate diagnosis and assessment of the extent of liver cirrhosis is vital in the diagnosis, treatment, and prognosis of the disease. Therefore, exploring a high value examination method to diagnose liver cirrhosis is very significant.

Research frontiers

It has been reported that liver cirrhosis can be divided into three classes according to the Child-Pugh (CP) scoring criteria, and the accuracy of their assessment methods have been demonstrated. Although liver biopsy is still currently the preferred diagnostic method for cirrhosis, the resulting trauma to the patient's body leads to low acceptance. Serum fibrosis indicators are a non-invasive examination method of cirrhosis diagnosis with a wide range of applications; however its accuracy in the assessment of cirrhosis degree remains to be studied. Acoustic radiation force impulse imaging (ARFI) is a new ultrasound elastography technique that can detect the hardness of the liver parenchyma for liver disease accurate assessment, and is non-invasive, simple, repeatable, and can effectively compensate for the lack of liver biopsy and serum liver fibrosis markers.

Innovations and breakthroughs

The clinical diagnostic value of AFRI-detected LS value for determining the degree of liver cirrhosis is high compared to the four indicators of serum liver fibrosis (HA, LN, PCIII, and IV-C). The diagnostic value of two combined diagnostics was more satisfactory compared to the indicators alone. Thus, detection by AFRI technology combined with the four indicators of serum liver fibrosis may serve as a powerful tool for determining liver cirrhosis degree, which has important clinical value and is worthy of wide promotion.

Applications

The diagnostic value of cirrhosis degree with PBC through liver cirrhosis degree assessment by ARFI combined with the four indicators of serum liver fibrosis is more satisfactory compared to the indicators alone and has important clinical application value. Results have shown that the higher the LS value, the higher the degree of liver fibrosis. This also confirmed that the diagnostic value of LS value was higher than that of the four indicators of liver fibrosis and, despite high diagnostic accuracy, that the diagnostic sensitivity and specificity were not stable. Further, the diagnosis value of liver cirrhosis degree for LS value combined with the four serum liver fibrosis was higher than each index alone.

Peer-review

The diagnostic value of cirrhosis degree with PBC through liver cirrhosis degree assessment by ARFI combined with the four indicators of serum liver fibrosis is more satisfactory compared to the indicators alone and has important clinical application value. The combination of AFRI and serum liver fibrosis four indicators can be used as a powerful tool to evaluate the degree of cirrhosis. It has important clinical application value and is worthy of clinical application.

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ISSN 1007-9327
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