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The Value of Combinational Elastography in Assessing Fibrosis Staging in Patients with Liver Fibrosis in Chronic Liver Disease

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Abstract: Objective: To investigate the value of ultrasound combined with elastography in the staging of fibrosis in patients with liver fibrosis in chronic liver disease. **Methods:** Eighty-nine patients with chronic liver disease diagnosed by liver puncture biopsy in the Affiliated Hospital of Youjiang Medical College of Nationalities from January 2021 to April 2024 were selected, and the patients were divided into three groups according to the Metavir score: cirrhosis group (F4, n=36), significant fibrosis group (F2-3, n=39), and no significant fibrosis group (F0-1, n=14). Clinical data and ultrasound combined elastography (Combi-Elasto) parameters were collected from all patients. One-way analysis of variance (ANOVA) was used to compare the differences in Combi-Elasto parameters among the three groups, and then ridge regression analysis was applied to further screen out the independent influencing factors of significant liver fibrosis. The staging accuracy of Combi-Elasto for the degree of liver fibrosis was assessed by the subjects' work characteristic curves (ROCs), which clarified the clinical value of Combi-Elasto. **Results:** The differences between the three groups comparing age, BMI, ATT, APRI, GPR, and FIB-4 among the groups were not statistically significant ($P > 0.05$), and the differences between the sexes, FIndex, and AIndex among the groups were statistically significant ($P < 0.05$). Spearman's correlation analysis revealed a positive correlation between FIndex, AIndex, FIB-4, APRI and GPR were significantly positively correlated with each other. One-way ANOVA and ridge regression analysis showed that AIndex and FIndex were independent influences on the occurrence of liver fibrosis, and ROC results showed that the AUCs of FIndex and AIndex in the group with no significant liver fibrosis were 0.836 and 0.855, respectively, and that the combination with APRI, GPR, and FIB-4 had the highest diagnostic efficacy in the group with no significant liver fibrosis. **Conclusion:** Ultrasound combined with elastography can significantly improve the diagnostic efficacy of the degree of hepatic fibrosis and provide a promising and innovative new method for identifying early hepatic fibrosis.

Keywords: Hepatic Fibrosis; Combinational Elastography; Chronic Liver Disease.

1. Introduction

Liver fibrosis is the excessive deposition of extracellular matrix (ECM) components, caused by chronic liver injury and sustained activation of the inflammatory response and fibrosis[1]. Early stages of the disease are often asymptomatic, but as fibrosis progresses, it can lead to structural and functional damage to the liver, resulting in cirrhosis and organ failure[2]. Many clinical studies have shown that early to mid-stage liver fibrosis is reversible with therapeutic interventions[3], thus, accurate assessment of liver fibrosis is crucial for patient prognosis, monitoring and management[4]. Currently, liver biopsy is still the gold standard for the diagnosis of liver fibrosis[4], but the complications caused by biopsy limit its application in the clinic[5], and liver fibrosis is a dynamic process[6], which requires frequent monitoring of the changes in liver texture to reflect the developmental stage of liver fibrosis, whereas liver tissue biopsy is not able to meet the clinical needs, therefore, the search for reliable and non-invasive methods of examination of liver fibrosis has become a clinical worker's Therefore, the aim of this study was to analyze the value of ultrasound combined with elastography in the assessment of liver fibrosis staging based on pathological staging.

2. Information and Methods

2.1. General Information

This study was reviewed and approved by the Ethics Committee of our university, and the subjects were 89 patients with hepatic fibrosis admitted to the Affiliated Hospital of Youjiang Medical College of Nationalities in our hospital from January 2021 to April 2024, including 74 males and 15 females aged 16-77 years old, who were divided into the cirrhosis group (F4, n = 36), significant fibrosis group (F2-3,n = 39), and no significant fibrosis group (F0-1, n = 14), according to the results of hepatic puncture biopsy as well as the Metavir score[7]. (1) Inclusion criteria: 1) patients with chronic liver disease diagnosed by liver puncture biopsy, and the duration of the disease ≥ 6 months; 2) complete Combi-Elasto examination data and pathological diagnostic staging data; 3) Liver puncture biopsy and Combi-Elasto examination need to be completed within 24 hours, and the same detection site. (2) Exclusion criteria: 1) Combi-Elasto quality does not meet the requirements (quality control VSN <90%, interquartile spacing (IQR)/median (Median) >30%); 2) patients with combined serious systemic diseases, such as cardiac insufficiency, renal failure or mental disorders. 3) Patients after liver transplantation.

2.2. Methodology

1. Assessment of the degree of hepatic fibrosis All patients

underwent ultrasound-guided percutaneous right lobe of liver tissue aspiration biopsy, the sampling location should try to ensure that the location of the elastography is the same as that of the hepatic aspiration biopsy, and an 18G-gauge biopsy needle was used to obtain at least 20-mm-long pathological tissue samples, and all the samples were treated with formalin solution fixation, and then subsequently paraffin-embedded was implemented to facilitate the slicing. Sections were further subjected to Masson's trichrome staining, reticulofibrillar special staining, and standard hematoxylin-eosin staining procedures. Staining was centrally examined by 2 liver pathologists, both of whom had more than 6 years of experience and had no knowledge of the combined elastography and clinical findings. Unqualified samples with a length of less than 20 mm and less than 6 confluent areas available for evaluation were strictly excluded. If the results of the readings were not uniform, the readings were repeated centrally until agreement was reached, and the degree of hepatic fibrosis was evaluated using the Metavir scoring system[7]: stage F4 was the early cirrhotic stage; stage F3 showed the presence of a large number of fibrous septa but not yet the formation of a sclerotic nodule; stage F2 showed fibrous dilatation of the confluent area but a limited number of fibrous septa had been formed; stage F1 demonstrated fibrosis of the confluent area, with no obvious formation of fibrous septa yet; F0 stage had no fibrosis.

2. Ultrasound Combined Elastography the Hitachi ARIETTA 850 ultrasonic instrument with C1-6 convex array probe was used, and was operated by a physician with rich experience in ultrasound elastography. During the examination, the combined elastography mode was selected, and Combi-Elasto was activated in the toolbar on the left side of the touch screen; the patient was placed in a horizontal supine position, and the operator placed the probe in the right intercostal liver, selected the measurement depth of 1~2 cm, and placed the sampling frame (which had been set in advance and did not need to be altered) in the right lobe of the liver (the best S5 segment, the S8 segment, or the S7 segment), to ensure that the direction of sampling was perpendicular to the horizontal line to avoid the intrahepatic occupancy and ductal structures, and instructed the physician during sampling to take a sample in the right lobe. When sampling, patients were instructed to hold their breath for 3 to 5 seconds under a calm respiratory state, and the data were collected after the strain curve had been displayed stably for 3 cycles, and the trough frames were selected for analysis; CombiElasto images were acquired from 5 different sections of the right lobe of the liver for each patient, and the average of the 5 measurements was calculated. The median was taken as the reference value. The F Index and A Index were taken as indicators of liver fibrosis. Quality control requirements: (1) the strain curve should be stabilized for 3 cycles; (2) VsN ≥ 90% to determine the reliability of the measured Vs value; (3) the median should be taken as the final result after 5 measurements, and the interquartile spacing (IQR)/median should be ≤ 30%.

2.3. Statistical Methods SPSS27.0 was Used to Process the Data

and the measured data were expressed as mean±standard deviation in conformity with normal distribution after confirming normality by Shapiro-Wilk test. Comparisons between groups were made according to the characteristics of the data, with one-way ANOVA for normality and chi-square, otherwise non-parametric tests such as Kruskal-Wallis were considered. one-way significant factors were used as independent variables, and the stage of hepatic fibrosis was the dependent variable, and a ridge regression model was established to analyze the influencing factors. The diagnostic performance of the model was assessed using ROC curves.

3. Results

3.1. General Information of Patients

The differences of age and BMI among the three groups were not statistically significant (P>0.05), and the differences of gender among the three groups were statistically significant (P<0.05). See Table 1.

Table 1. Descriptive statistics and intergroup comparisons of the general data of the three groups of patients

norm	no significant fibrosis group(*n* = 14)	significant fibrosis group (*n* = 39)	cirrhosis group(*n* = 36)	*F*/*H*/x^2	*P*
BMI(kg/m²)	22.99±3.22	22.84±3.14	21.88±2.73	1.194	0.308
age (years)	45.00(38.00,49.00)	48.00(41.25,56.00)	45.50(43.50,55.00)	2.856	0.240
sex[*n*(%)]	-	-	-	8.06	<0.05
male	8 (57.14)	34 (87.18)	32 (88.89)	-	-
female	6 (42.86)	5 (12.82)	4 (11.11)	-	-

3.2. Patient Combi-Elasto Parameters

The results of one-way ANOVA showed that the differences in F Index and A Index were statistically significant between the groups (p < 0.05). See Table 2.

3.3. Regression Analysis of Patients Developing Significant Liver Fibrosis

A regression model (K=0.21) was established with F Index and A Index as independent variables and liver fibrosis stage as dependent variable (assigned values: 2= cirrhosis, 1= significant liver fibrosis, 0= no significant liver fibrosis) in Table 2. The results showed that F Index and A Index were

the risk factors for patients to develop significant liver fibrosis ($P < 0.05$). See Table 3.

Table 2. Descriptive statistics and intergroup comparison of Combi-Elasto parameters in the three groups of patients

norm	no significant fibrosis group(n = 14)	significant fibrosis group (n = 39)	cirrhosis group (n = 36)	F	P
F Index	1.62±0.58	2.34±0.63	2.62±0.64	12.879	<0.001
A Index	1.09±0.30	1.48±0.27	1.61±0.30	16.081	<0.001

Table 3. Ridge regression analysis of patients developing significant liver fibrosis

K=0.21	Unstandardized coefficient		Standardized coefficient	t	P	R^2	Adjustment of R^2	F
	B	standard error	Beta					
Constant	0.002	0.250	-	0.009	0.993	0.231	0.213	12.886(0.000***)
F Index	0.155	0.072	0.154	2.149	0.034**			
A Index	0.601	0.152	0.283	3.952	0.000***			

3.4. Analysis of the Diagnostic Efficacy of Each Model on the Degree of Liver Fibrosis

In this study, patients were initially divided into three groups: non-significant fibrosis group (F0-1), significant fibrosis group (F2-3) and cirrhosis group (F4). In order to assess the diagnostic model's ability to identify the stage of fibrosis that requires clinical intervention and to meet the requirement of ROC analysis for dichotomous classification, the significant fibrosis group (F2-3) and the cirrhosis group (F4) were merged into the "significant fibrosis group (F2-4)" by reference to a previous study[8], which was compared with the non-significant fibrosis group (F0-1) Comparison was made. The area under the curve (AUC) of the diagnostic model for liver fibrosis staging was analyzed by plotting the ROC curve to assess its diagnostic efficacy. Meanwhile, the optimal diagnostic cutoff value of the model was determined using the Jordon index, and the corresponding diagnostic indexes such as sensitivity and specificity were calculated, as shown in Table 4 and Figure 1.

Table 4. Results of ROC curve analysis for each diagnostic model to identify the non-significant fibrosis group (F0-1) from the significant fibrosis group (F2-4)

mould	Sensitivity (%)	Specificity (%)	Jordon index	truncation value	AUC	95%CI	P
F Index	80.00	78.57	0.586	1.87	0.836	0.743~0.906	<0.001
A Index	81.33	78.57	0.599	1.30	0.855	0.764~0.920	<0.001

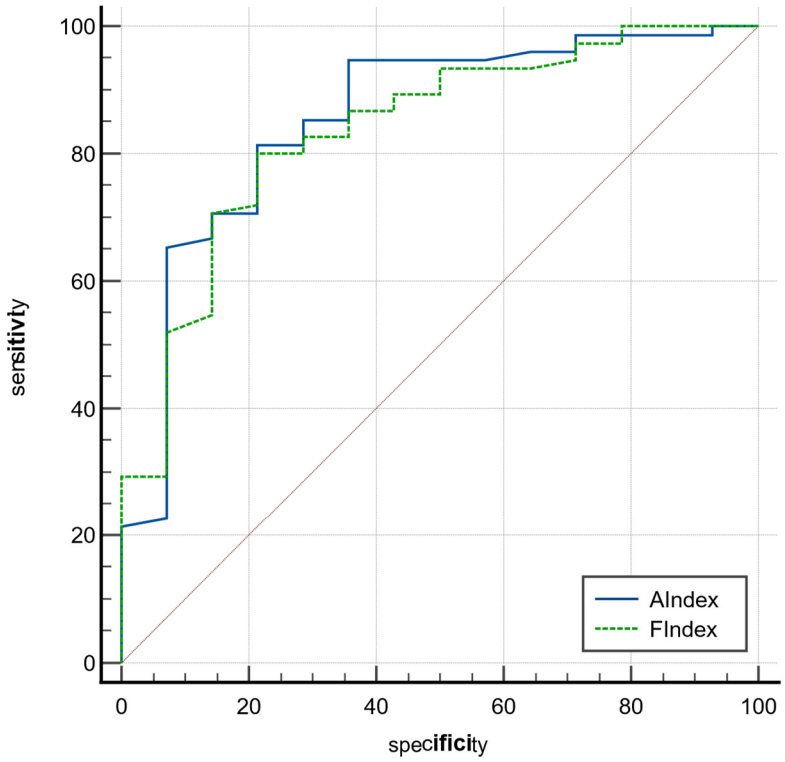

Figure 1. Comparison of ROC curves for each diagnostic model to identify the non-significant fibrosis group (F0-1) versus the significant fibrosis group (F2-4)

4. Discussion

Numerous studies have identified fibrosis as an end stage of chronic liver disease, associated with alcohol-related liver disease (ALD), metabolism-related liver disease, viral hepatitis, and hepatic autoimmune disorders[9], which can progress to cirrhosis or even hepatocellular carcinoma

without appropriate intervention[2]. Some studies have proposed that early liver fibrosis is reversible in pathological process and timely scientific diagnosis and effective treatment can significantly delay or stop the irreversible development of liver failure. Liver fibrosis is the formation of scar tissue in the liver when inflammation persists for a long period of time. Evaluation of liver fibrosis is critical for predicting the prognosis of chronic liver diseases and managing patients with these diseases. Although liver biopsy remains the gold standard for assessing liver fibrosis, it is limited by its invasive nature. Therefore, there are ongoing efforts to develop non-invasive methods for assessing liver fibrosis, including imaging techniques and serum biomarkers.

The mainstream elastography techniques currently used to assess liver fibrosis in clinical practice include real-time tissue elastography (RTE), transient elastography (TE), point shear wave elastography (pSWE), and two-dimensional shear wave elastography (2D-SWE). Each of these techniques has its own characteristics, but there are certain application limitations. Clinical observations revealed that 2D-SWE showed better clinical value in the evaluation of liver fibrosis staging in patients with chronic hepatitis B, and its diagnostic accuracy was better than that of traditional ultrasonography. However, it should be noted that SWE results may be affected by various factors, including differences in equipment parameters, the degree of hepatic steatosis, the patient's obesity status, and fluctuations in ALT levels. In contrast, the RTE technique is able to reduce the interference of inflammatory factors through tissue diffusion quantitative analysis, thus providing more reliable data for liver fibrosis assessment. The Combi-Elasto technique, which has emerged in recent years, combines the advantages of shear-wave elasticity and strain elasticity to enable joint multiparameter analysis. Strain elasticity data and shear wave elasticity parameters can be acquired synchronously by the technique and then translated into a composite score by the chronic liver disease model. The technique is characterized by the simultaneous provision of FI values for liver fibrosis, acoustic attenuation coefficients for steatosis, and AI values for inflammatory activity, which provides a new technological solution for the comprehensive assessment of chronic liver disease.

In this study, the results of one-way analysis of variance (ANOVA) showed that the differences between F Index and A Index were statistically significant ($P<0.001$) among the three groups of non-significant fibrosis group (F0-F1), significant fibrosis group (F2-F3), and cirrhosis group (F4), and the values of the two indexes showed a significant upward trend with the aggravation of the degree of fibrosis. This finding suggests that the F Index and A Index may have high sensitivity and validity in assessing the degree of hepatic fibrosis, and can be used as important reference indexes to distinguish between different stages of fibrosis. Ridge regression analysis showed that both F Index and A Index were independent predictors of significant hepatic fibrosis, and the predictive power of A Index was significantly better than that of F Index, which was consistent with the pathological mechanism of hepatic fibrosis: in chronic liver disease, persistent inflammation precedes the formation of fibrosis, and activation of hepatic stellate cells after the formation of hepatic fibrosis further increases the secretion of a large number of inflammatory mediators, and the activation of hepatic stellate cells after the formation of liver fibrosis further increases the secretion of a large number of inflammatory mediators. The activation of hepatic stellate cells after the formation of hepatic fibrosis will further increase the secretion of a large number of inflammatory mediators, which suggests that the A Index (reflecting inflammatory activity) may be able to predict the progression of hepatic fibrosis at a much earlier stage and more sensitively than the F Index (reflecting the degree of fibrosis).

In this study, the diagnostic value of different models for liver fibrosis staging was evaluated by ROC curve analysis, and the results showed that both the F Index and the A Index demonstrated good diagnostic efficacy (AUC of 0.836 and 0.855, respectively), with the A Index being slightly better than the F Index. This result suggests that the Liver Inflammatory Activity Index may be a more sensitive index than the Hepatic Fibrosis Index in reflecting the early stage of fibrosis progression. In a study by Chen Biwu [8] and others, the diagnostic efficacy of the Combi-Elasto technique, which integrates multiple parameters, was shown to be significantly better than that of transient elastography (TE) for the diagnosis of ≥S1 stage liver fibrosis (AUC=0.936).

Studies have shown that ultrasound elastography has been widely used in the staging assessment of liver fibrosis, mainly due to its advantages of noninvasiveness, simplicity of operation and economy. However, it is worth noting that each type of elastography has its own characteristics and limitations in clinical application, and the rational selection and application of these techniques are essential to improve the diagnostic efficacy. Combi-Elasto technique has shown high efficacy in the assessment of hepatic fibrosis, especially in the early stage of non-significant fibrosis. Based on its superior diagnostic performance, the authors recommend the Combi-Elasto technique as a screening tool for early hepatic fibrosis, with a view to achieving early identification and treatment, thus providing significant clinical value for reversal of the condition. Future studies should further optimize the application scenarios of this technique and verify its stability and generalizability in larger samples and diverse clinical settings.

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