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• CLINICAL RESEARCH •

Grading and staging of hepatic fibrosis, and its relationship with noninvasive diagnostic parameters

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Abstract

AIM: To explore the grade and stage of pathology and the relationship between grading and staging of hepatic fibrosis and noninvasive diagnostic parameters.

METHODS: Inflammatory activity and fibrosis of consecutive liver biopsies from 200 patients with chronic liver disease were determined according to the Diagnostic Criteria of Chronic Hepatitis in China, 1995. A comparative analysis was made in these patients comparing serum markers, Doppler ultrasonography, CT and/or MR imaging with the findings of liver biopsy.

RESULTS: With increase of inflammatory activity, the degree of fibrosis also rose. There was a close correlation between liver fibrosis and inflammatory activity. AST, GGT, albumin, albumin/globulin, ALP, AFP, hyaluronic acid, N-terminal procollagen III(P III NP), collagen type IV(Col IV), tissue inhibitors of metalloproteinases-1(TIMP-1), alpha-2-macroglobulin, natural killer cells(NK), some parameters of Doppler ultrasonography, CT and/or MR imaging were all related to the degree of inflammatory activity. GGT, albumin, albumin/globulin, ALP, AFP, hyaluronic acid, Col IV, TIMP-1, alpha-2- macroglobulin, transforming growth factor-beta 1(TGFβ1), NK, some parameters of Doppler ultrasonography, CT and/or MR imaging were all related to the staging of fibrosis. By regression analysis, the parameters used in combination to differentiate the presence or absence of fibrosis were age, GGT, the parameter of blood flow of portal vein per minute, the maximum oblique diameter of right liver by B ultrasound, the wavy hepatic surface contour by CT and/or MR. The sensitivity, specificity and accuracy of the above parameters were 80.36 %, 86.67 %, and 81.10 %, respectively.

CONCLUSION: There is close correlation between liver fibrosis and inflammatory activity. The grading and staging of liver fibrosis are related to serum markers, Doppler ultrasonography, CT and/or MR imaging. The combination of the above mentioned noninvasive parameters are quite sensitive and specific in the diagnosis of hepatic fibrosis.

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INTRODUCTION

Hepatic fibrosis has been a common response to chronic liver injury and might result in potentially lethal sequelae[1-3]. In chronic liver diseases, determination of stage and activity of the fibrotic process and evaluation of anti-fibrotic treatment required accurate variables, the commonly so-called ' fibrotic markers' [4-11]. Since the value of laboratory test to diagnose liver fibrosis was limited, biopsy has been still the golden criterion of the diagnosis of liver fibrosis and cirrhosis at present[12,13]. But it is an invasive diagnostic method, so its application and further propagation are somewhat limited. Searching for a noninvasive diagnostic approach is an interesting subject both at home and abroad. Although some parameters have been found to have important values in iconography and laboratory tests, they are still far from satisfactory. So it is of great realistic value to explore a credible, specific, and noninvasive diagnostic parameter of liver fibrosis for the prevention and treatment of chronic liver disease[14-28]. Therefore, on the basis of histology of chronic liver diseases, this study was designed to explore the relationship between the grade and stage of pathology, and noninvasive diagnostic parameters. We hoped that we could provide the basis for the noninvasive diagnosis of liver fibrosis, so as to improve the prevention and treatment of liver fibrosis.

MATERIALS AND METHODS

Selection of patients

The study was organized and carried out by Shanghai Cooperative Group of Hepatic Fibrosis Project. The Cooperaitive Group was led by Renji Hospital and Changhai Hospital in Shanghai. Cases collected by the Cooperative Group were 37 from Changhai Hospital, 36 from Renji Hospital, 30 from Putuo District Central Hospital, 22 from Shanghai Liver Disease Center of Nanjing Military Command, 20 from Changzheng Hospital, 14 from Zhongshan Hospital,

11 from Huashan Hospital, 9 from Shibei Hospital, 8 from Shanghai No.6 Hospital, 6 from Shanghai Infectious Disease Hospital, 3 from Ruijin Hospital, 3 from Shanghai No.9 hospital, and 1 from Shanghai No.1 hospital. A total of 200 patients were collected between July and October in 1999 according to both clinical and pathological criteria. There were 156 males and 44 females with an average age of 34 years (range 15-60).

Histological examination

One week after admission, all patients underwent liver puncture biopsy under the guide of B type ultrasound with the 14G Quick-cut needle (8-Light Company, Japan) or Menghini needle. The length of liver specimen was more than 1 cm. The samples were fixed with 10 % formaldehyde, paraffin slides were made and stained with hematoxylin-eosin, reticular fiber and collagen fiber according to the grading and staging of Diagnostic Criteria of Chronic Hepatitis in China in 1995[29]. Eleven patients were graded and staged for inflammatory activity and liver fibrosis. Three pathologists read the slide independently. The results were checked with Kappa test by statistical experts. It was shown that the coherence of grading and staging of hepatitis fibrosis was excellent. The pathological diagnosis of liver biopsy was finally made by the Department of Pathology , Medical Collage of Fudan University.

Laboratory tests

Blood and urine routine tests: α-fetoprotein(AFP) and prothrombin time were examined by the Cooperative Units.

Serum biochemical tests: Total bilirubin, indirect bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), AST/ALT, γ-glutamyl transpeptidase(GGT), alkaline phosphatase(ALP), albumin, albumin/globulin, blood urea nitrogen(BUN), creatinine(Cr), triglyceride, cholersterol, high density lipoprotein and low density lipoprotein were all measured by Shanghai Institute of Digestive Disease.

Markers of hepatitis virus and immunological parameter: HBsAg, Anti-HBs, HBeAg, Anti-HBe, Anti-HBc, HBV- DNA, Anti-HCV, HCV- RNA, $CD3^+$, $CD4^+$, $CD8^+$, natural killer cell (NKC), interleukin-2 (IL-2), and interferon-γ (IFN-γ) were detected by Shanghai Institute of Digestive Disease.

Related liver fibrosis markers: α-2-macroglobulin(α-MA), transferrin, apolipoproteinA1, hyaluronic acid (HA), laminin, N-terminal procollagen III(PIIINP), 7S collagen IV (7S-IV), and transforming growth factor-β1(TGF-β1) were detected by the Clinical Immunology Center of Changzheng Hospital in Shanghai.

Tissue inhibitor of metalloproteinase-1(TIMP-1) were assayed by Shanghai Hongqiao Medical Reagent Institute.

B ultrasound examination

All B ultrasound examinations of the patients were carried out in Shanghai Institute of Digestive Disease. The patients had empty stomach for 14 hours before examination. Two skillful doctors performed the examination with color Doppler ultrasonic instrument(HDI 5000). The results were saved in compact disk, three experts judged the examination results and made the final reports.

CT and/or MR imaging

All CT and/or MR examinations were performed by Ruijin Hospital, Changzheng Hospital, Changhai Hospital, Zhongshan Hospital, and Shanghai No.6 Hospital in the Cooperative Group. CT scanners with PQ-2000 and/or PQ-5000 (Picker Company), Plus-s (Siemens Company), Hispeed Adv (GE Company), and MR scanners with Cyroscan T10-NT (Philips Company),Vision Plus and Magnetron Impact (Siemens Company) were used.

Statistical analysis

All the data were analyzed with SAS software by Statistical Department in Shanghai Second Medical University.

RESULTS

Histological examinations

It was revealed that there was a significantly positive correlation between the inflammatory activity and the staging of liver fibrosis. With increase of inflammatory activity, liver fibrosis became more serious (Table 1).

Table 1 Pathological diagnostic results of 200 liver biopsy samples

Staging of fibrosis	Grading of inflammation					value	
	1	2	3	4	Total	χ^2-value	*P*-value
0	18	2	0	0	20	278.3	1E-04
1	42	22	0	0	64		
2	6	33	26	0	64		
3	9	2	19	4	25		
4	0	0	3	23	26		
Total	66	59	48	27	200		

Laboratory examinations

Relationship between serum biochemical parameters and the grading of inflammation: Only serum biochemical parameters related to liver inflammation are listed in Table 2.

Table 2 Relationship between serum biochemical parameters and grading of inflammation

Parameter	Comparision among groups of inflammation grading					
	1-2	1-3	1-4	2-3	2-4	3-4
RBC			b		b	b
PLT			b		b	b
AST		b	b	a	b	
GGT	a	b	b	b	b	
Albumin			b		b	b
Albumin / globulin			b		b	b
ALP			b		b	
AFP	b	b	b	b	b	b
HA	b	b	b	b	b	b
PIIINP			b		b	
7S-IV		a	b	a	b	
TIMP-1		a	a			
α-MA			b		a	
NK			b		a	a
IgG			b		b	b
IgG+IgA+IgM			b		b	b

$^aP<0.05$, $^bP<0.01$.

Relationship between serum biochemical parameters and staging of liver fibrosis: Only the serum biochemical parameters related to liver fibrosis are listed in Table 3.

B ultrasound examinations

Comparison between parameters of ultrasonic 2-D and color Doppler flow image and the groups of inflammation grading: Only the parameters of ultrasonic 2-D and color Doppler flow image related with the groups of inflammation grading are listed in Table 4.

Comparison between parameters of ultrasonic 2-D and color Doppler flow image and groups of liver fibrosis staging: Only the parameters of ultrasonic 2-D and color Doppler flow image related with the groups of liver fibrosis staging are listed in Table 5.

CT and/or MR imaging examination

Among the 200 patients who received liver biopsy, 192 patients had CT and/or MR imaging examintion. Twenty cases (10.4 %) received both CT and MR imaging examination, 92cases (47.9 %) received only CT examination, 80 cases (41.7 %)

Table 3 Relationship between serum biochemical parameters and staging of liver fibrosis

Parameter	Comparision among groups of liver fibrosis staging									
	0-1	0-2	0-3	0-4	1-2	1-3	1-4	2-3	2-4	3-4
RBC				a			a		a	a
GGT		b	b	b	b	b	b			
Albumin				b			b		b	b
Albumin / globulin				b			b		b	b
ALP				b			a			
AFP			b	b		b	b		b	
HA		b	b	b	b	b	b		b	b
7S-IV				a			a		a	
TIMP-1			a	b		a	a			
α-MA				a			b		a	
TGFβ-1	a	a	a	a						
IgG				b			b		b	b
IgG+IgA+IgM				b			b		b	b

[a]$P<0.05$, [b]$P<0.01$.

Table 4 Comparison between parameters of ultrasonic 2-D and color Doppler flow image and groups of inflammation grading

Parameter	Comparision among groups of inflammation grading					
	1-2	1-3	1-4	2-3	2-4	3-4
Inner diameter of left portal vein		a				
Inner diameter of middle liver vein			a		a	
Inner diameter of right liver vein			b		a	
Thickness of gallbladder wall		a	b	a	b	
Shape of gallbladder			b		b	
Vertical diameter of spleen		a	b	a	b	a
Thickness of spleen		a	b	a	b	
Diameter of spleen vein			b		a	
Thickening of the light dots in liver substance			b		b	
Movement degree along with breath			b		a	
Movement degree along with heart beat			b		a	
Blood stream velocity in constriction phase of liver artery		a				
Blood stream velocity in dilation phase of liver artery			a			

[a]$P<0.05$, [b]$P<0.01$.

Table 5 Comparison between parameters of ultrasonic 2-D and color Doppler flow image and groups of liver fibrosis staging

Parameter	Comparision among groups of liver fibrosis staging									
	0-1	0-2	0-3	0-4	1-2	1-3	1-4	2-3	2-4	3-4
Thickness of liver capsule				a						
Maximum oblique diameter of right liver	a	b	b	b						
Tube diameter of portal vein trunk		a		a						
Inner diameter of left portal vein	a	b	b	a						
Inner diameter of right portal vein	a	a	a	a						
Thickness of gallbladder wall				b			b		a	a
Shape of gallblader				b			a		a	a
Diameter of splenic vein				b			a			a
Vertical diameter of spleen			a	b			b		a	
Thickness of spleen				a						
Thickening of the light dots in liver substance		a		b			a			
Movement degree along with breath				b			a			
Movement degree along with heart beat									b	a
Parameter of blood flow of portal vein per minute	a	a	a	a						

[a]$P<0.05$, [b]$P<0.01$.

received only MR examination.

The results demonstrated that the longitudinal diameter of the left lobe, volume index, the wavy hepatic surface contour, liver crack widening, size of the gallbladder, thickening of the gallbladder wall, changes like little bursa of peri-gallbladder tube, to and fro diameter of the spleen, and thickness of the spleen were all correlated with the grading of inflammation. The wavy hepatic surface contour, changes like little bursa of peri-gallbladder tube, and the to and fro diameter of the spleen were correlated with the staging of liver fibrosis.

DISCUSSION

At present, the diagnosis of liver fibrosis still depends on pathological examination of liver puncture tissue. Since the procedure is invasive, its application and extensive use in clinical practice are still limited. So great attention has been paid to search for and clinical study of a non-invasive diagnostic parameter for liver fibrosis[15,27,28]. It would not only speed up the study of basic medical theory about liver disease, but also be of value[1,3].

In 1995, a new pathological classification method was carried out in our country[29]. The criteria were established respective to distinguish inflammation from liver fibrosis by grading and staging. Both of them have quantified parameters, which are convenient for statistical analysis. Following these criteria, we compared pathological classification with some non-invasive parameters (serologic and imaging parameters), so as to evaluate the value and significance of different parameters in reflecting pathological changes. In the liver puncture tissue of 200 patients with chronic hepatitis, there was a significant positive correlation between inflammatory activity and staging of liver fibrosis. With the increase of inflammatory activity, liver fibrosis became more serious.

In serology, RBC, PLT, AST, GGT, albumin, albumin/globulin, ALP, AFP, HA, PIIINP, 7S-IV, TIMP-1, α2-MA, NK, *etc*. had a relationship with inflammatory activity, but GGT, albumin, albumin/globulin, ALP, AFP, HA, 7S-IV, and α2-MA had a relationship with liver fibrosis. So these latter parameters might be used as the parameters of liver fibrosis[5,10,30-34]. With the development of inflammation and fibrosis, the level of HA and 7S-IV rose gradually in different inflammatory grading and liver fibrosis staging. In pathological diagnosis, Stage 1 and Stage 2 indicated mild fibrosis, Stage 3 and Stage 4 indicated severe fibrosis. The accuracy, specificity and sensitivity of HA were 82.9 %, 93 %, and 56 %, respectively. The accuracy, specificity and sensitivity of 7S-IV were 72.4 %, 94.3 %, and 18 %, respectively. To some extent, PIIINP might reflect mild and severe changes of inflammation, but it might not reflect the fibrotic changes. This study revealed that laminin had no diagnostic value either in inflammation or in fibrotic changes. It was found that the level of TGFβ1 and TIMP-1 increased more significantly in inflammation and early stage of fibrosis, indicating that they could reflect the changes of liver inflammation and fibrosis[35-38]. In this study, PIIINP, laminin, transferrin, and apoproteinA1 which were known to have significant diagnostic value, were not confirmed. So, we should do more work to probe into their diagnostic significance. In the following study, we would increase the number of cases to further study the diagnostic value of the related parameters in liver fibrosis and evaluate the efficacy of anti-fibrotic drugs, so as to provide a sound basis for the reasonable combined use of the different parameters, and to improve the specificity, accuracy and sensitivity of noninvasive diagnostic tests for liver fibrosis[3,15,19,28].

With the development of modern medical imaging techniques, ultrasound, CT and MR would be widely used. These methods could significantly improve the diagnosis and differential diagnosis of liver disease[17,18,20-26]. In this study, ultrasound examination indicated that the thickness of liver capsule, maximum oblique diameter of right liver, tube diameter of portal vein trunk, diameter of left portal vein, diameter of right portal vein, thickness of gallbladder wall, thickness of spleen, diameter of splenic vein, parameter of blood stream quantity per minute in portal vein, light dot shape, and shape of gallbladder were correlated with the staging of liver fibrosis. CT and/or MR imaging only revealed that the volume of spleen was correlated with liver fibrosis. The results demonstrated that B ultrasound had more value than CT and/or MR imaging in the diagnosis of liver fibrosis. This of course needs further study. It should be noted that factors such as individual variation, nature of the instrument used, patient' s condition at the time of examination and difference of the performer' s skill might affect the evaluation of the result[21-24]. At the same time, we should carry out quantitative and/or semi-quantitative research on ultrasonic two-dimensional imaging and Doppler blood stream, so as to increase the sensitivity, specificity and accuracy of the diagnostic parameters.

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