

## Influence factors of serum fibrosis markers in liver fibrosis

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### Abstract

**AIM:** To analyze the factors which influence the serum levels of hyaluronic acid (HA), type III pro-collagen (PCIII), laminin (LN) and type IV collagen (C-IV) in liver fibrosis.

**METHODS:** The serum specimens from 141 chronic hepatitis patients were assayed for fibrosis indexes including HA, PCIII, LN and C-IV with radioimmunoassay (RIA) and liver function indexes by an automatic biochemistry analyzer. The patients were then divided into consistent group and inconsistent group. The patients' clinical manifestations were recorded, routine blood pictures were done by a blood counter and analyzer (AC-900). Liver biopsy specimens were examined path-morphologically. The inner diameters of portal vein, splenic vein and thickness of spleen were all measured by ultrasonography.

**RESULTS:** Sixteen patients (14.16 %) had serum fibrosis indexes inconsistent with histological stage of their hepatic fibrosis. Their serum fibrosis indexes did not correlate with the stage of hepatic fibrosis ( $P>0.05$ ), but were positively correlated with the grade of inflammation ( $\chi^2=12.07, P<0.05$ ). At the same time, serum albumin (ALB) and the ratio of albumin and globulin (A/G) were significantly increased ( $t=3.06, P<0.01$ ), ( $t=3.70, P<0.01$ ). Serum levels of glutamic-pyruvic transaminase (ALT), glutamic-oxaloacetic transaminase (AST),  $\gamma$ -glutamyl transferase (GGT) and globulin (GLB) were all significantly decreased ( $t=2.45, P<0.05$ ), ( $t=2.33, P<0.05$ ), ( $t=2.08, P<0.05$ ), ( $t=3.03, P<0.01$ ). Weary degree also decreased more obviously ( $\chi^2=7.52, P<0.05$ ), but other clinical manifestations, routine blood indexes, serum levels of alkaline phosphatase (AKP), total bilirubin (TBIL), total protein (TP), width of main portal vein, width of splenic vein and thickness of spleen had no significant change ( $P>0.05$ ).

**CONCLUSION:** Serum fibrosis indexes can be influenced by the grade of inflammation, some liver function indexes and clinical manifestations. Comprehensive analysis is necessary for its proper interpretation.

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### INTRODUCTION

Many chronic injuries can lead to fibrosis of liver<sup>[1-11]</sup>. Hepatic

fibrosis is resulted from the loss of normal liver cell function due to disorganized over-accumulation of extra-cellular matrix (ECM) components in the liver<sup>[12-17]</sup>. It is clear that the increased production and degradation of ECM components are responsible for the altered ECM metabolism. Liver biopsy has traditionally been the standard method for assessing hepatic fibrosis, but the procedure is invasive in nature and has complications though with a low incidence. So its popularity is somewhat hindered. Reports showed that serum fibrosis indexes, including HA, PCIII, LN, C-IV and others, could reflect the activity of hepatic fibrosis to some extent<sup>[18-27]</sup>. Mean  $\pm$  SD has always been used to express the standard for hepatic fibrosis. We have explored the clinical significance of the four serum fibrosis indexes by detecting them in 2 600 patients with chronic hepatitis including 280 patients undertaken biopsy<sup>[28,29]</sup>. At same time, patients whose four serum fibrosis indexes were not consistent with the degree of hepatic fibrosis were found, so we selected these patients to analyze what factors might influence the four serum fibrosis indexes (HA, PCIII, LN and C-IV) in diagnosing liver fibrosis.

### MATERIALS AND METHODS

#### Subjects

During the Sixth National Conference for Infectious and Parasitic Diseases, the protocol of prevention and treatment for virus hepatitis was modified in 2000 (abbreviated as "2000 criteria")<sup>[30]</sup>. One hundred and forty-one patients had typical presentations of chronic hepatitis, 121 were males and 20 females. There were mild, moderate and severe degrees of the disease in the group. Case histories were mainly collected from the First Affiliated Hospital, School of Medicine, Zhejiang University. Some were from other hospitals in Zhejiang Province between July, 1998 and May, 2000. The age ranged from 18 to 62 years, the average age was  $38.75\pm 14.53$ . Weary Degree: 0: did not feel weary; 1: could join routine activities, but felt weary; 2: could join light work, but felt weary; 3: could not work, felt weary while moving. The disease course was from one to 30 years.

#### Clinical manifestations

Total volume of food taken by the patient every day, length of liver and spleen under costal margin were recorded. The criteria of clinical manifestations were as following: (1). Weary degree: as stated above. (2). Degree of abdominal distension: 0: did not feel abdominal distension; 1: felt abdominal distension while taking food or abdominal distension usually; 2: felt abdominal distension while taking a little food, but can endure; 3: felt abdominal distension, did not want to take food, felt abdominal distension while taking food, can not endure. (3). Secret anguish degree: 0: did not feel secret anguish; 1: felt secret anguish, but could take food; 2: felt secret anguish, could endure; 3: felt secret anguish, could not endure, needed medication.

#### Histology

The needles (18G) were purchased from Angiomed Corporation in German. The length of liver biopsy specimen exceeded 1 cm. Biopsy fragments of the livers were fixed in 10 % neutralized formaldehyde, embedded in paraffin, and then stained with hematoxylin and eosin. Reticulum fibrosis

stain and Sirius red method were used specially for staining fibrous tissue components. Histological assessment of the liver was done according to Wang's report<sup>[31]</sup>, and staging of fibrosis was divided into four, expressed as S1 to S4 according to the "2000 criteria"<sup>[30]</sup>. S0 showed no fibrosis. S1 showed expansion in portal tract areas with fibrosis. S2 showed fibrosis around portal tract areas with formation of fibrosis segregation while maintain lobular structure. S3 showed formation of fibrosis segregation and disorder of lobular structure without hepatic cirrhosis, and S4 showed early stage or confirmed cirrhosis.

#### Determination of serum fibrosis tests and liver function indexes

The serum specimens from 141 chronic hepatitis patients were stored at -20 °C. Assay of the levels of serum HA, PCIII, C-IV and LN was done by RIA. The kits of HA, C-IV and LN were provided by the Shanghai Navy Medical Institute. The kit of PCIII was supplied by the Chongqing Tumor Institute. The procedures were performed according to the user's manual. The assay of liver function indexes was measured by an automatic biochemistry analyzer, these indexes included total bilirubin (TBIL), glutamic-pyruvic transaminase (ALT), glutamic-oxaloacetic transaminase (AST),  $\gamma$  glutamyl-transferase (GGT), alkaline phosphatase (AKP), total protein (TP), albumin (ALB), globulin (GLB) and the ratio of albumin and globulin (A/G).

#### Determination of routine blood indexes

Blood samples were drawn from the veins and treated with EDTA-K<sub>2</sub> (the concentration was 1.5 mg/ml). WBC, RBC and platelet were determined by a blood cell counter and analyzer (AC-900).

#### Ultrasonic examination

All patients were forbidden to take water and food for eight hours before examination. Inner diameters of the portal vein, splenic vein and thickness of the spleen were measured, all the procedures were performed by the same physician.

#### Definition of patients whose serum fibrosis indexes were inconsistent with histologic staging of their hepatic fibrosis

All patients were divided into two groups. If in S $\geq$ 2 group, all four serum fibrosis indexes were less than or equal to the mean value of that in S1 group, these patients would then be classified as inconsistent group. On the contrary, they would be classified as the consistent group. There was also inconsistency in a single index, that meant staging belonged to S $\geq$ 2, but the index was less than or equal to the mean of that in S1 group.

#### Statistical analysis

Results were expressed as mean  $\pm$  standard deviation ( $\bar{x}\pm s$ ) and *t* test was done when necessary, nonparametric one-way ANOVA was used for nonparametric data, all tests were done by SPSS 10.0 statistical program and considered statistically significant at *P*<0.05.

## RESULTS

#### Inconsistency between each serum fibrosis index and stage of hepatic fibrosis

When hepatic fibrosis was in stage 1, the mean of HA was 187.23 ng/ml, LN was 144.68 ng/ml, PCIII was 151.42  $\mu$ g/L, and C-IV was 74.26  $\mu$ g/L. One hundred and thirteen patients were found in hepatic fibrosis stage II or more than that, 33 cases were inconsistent with staging of hepatic fibrosis for HA. More cases were inconsistent for C-IV, 43 cases were inconsistent with staging of hepatic fibrosis for LN (Table 1).

**Table 1** Inconsistency between each serum fibrosis index and stage of hepatic fibrosis

Stage (S)	n	HA	C-IV	PCIII	LN
S2	30	13	14	16	17
S3	31	9	10	10	11
S4	52	11	12	13	15
Total	113	33 (29.20%)	36(31.86%)	39(34.51%)	43 (38.05%)

#### Distribution of patients whose four serum fibrosis indexes were inconsistent with stage of hepatic fibrosis

Among 113 patients, 16 (14.16 %) were in inconsistent group and 97(85.84 %) in consistent group, no significant difference was found in staging of hepatic fibrosis between two groups (*P*>0.05), (Table 2).

**Table 2** Staging comparison between two groups

Groups	Stage of hepatic fibrosis		
	S2	S3	S4
Consistent group	24	27	46
Inconsistent group	6	4	6

$\chi^2=1.18$ , *P*>0.05.

#### Inflammation grading of patients in inconsistent group

Table 3 shows that inflammation grade was mainly G2 in inconsistent group, while mainly G3 and G4 in consistent group. The difference was significant between two groups (*P*<0.05).

**Table 3** Comparison of inflammation grade between two groups

Groups	Inflammation grade			
	G1	G2	G3	G4
Consistent group	5	17	49	26
Inconsistent group	1	9	4	2

$\chi^2=12.07$ , *P*<0.05.

#### Clinical manifestations in inconsistent group

Table 4 and table 5 show no patient whose degree of weary, abdominal distension and secret anguish exceeded 2 in consistent group. There was no patient whose degree of weary, abdominal distension and secret anguish exceeded 1 in inconsistent group. The daily food volume of the patients increased slightly, the palpable length of liver and spleen decreased slightly. The difference was not significant between two groups (*P*>0.05) except weary degree (*P*<0.05).

**Table 4** Comparison of clinical manifestations between two groups

Groups	Weary degree			Abdominal distension degree			Secret anguish degree		
	0	1	2	0	1	2	0	1	2
Consistent group	39	41	17	72	24	1	86	8	3
Inconsistent group	12 <sup>a</sup>	4	0	14	2	0	16	0	0

$\chi^2=7.52$ , *P*<0.05.

**Table 5** Comparison of clinical manifestations between two groups ( $\bar{x}\pm s$ )

Groups	n	Volume of food(g)	Length of liver (cm)	Length of spleen(cm)
Consistent group	97	427.11 $\pm$ 194.15	0.31 $\pm$ 0.63	0.53 $\pm$ 0.85
Inconsistent group	16	456.25 $\pm$ 160.08	0.28 $\pm$ 0.55	0.34 $\pm$ 0.60

### Change of routine blood indexes in inconsistent group

No significant difference was found in WBC, RBC and PLT between two groups ( $P>0.05$ ), (Table 6).

**Table 6** Comparison of routine blood tests between two groups ( $\bar{x}\pm s$ )

Groups	n	WBC	RBC	PLT
Consistent group	97	5.07±1.12	4.61±0.52	116.52±34.14
Inconsistent group	16	4.90±1.24	4.64±0.57	117.00±26.38

### Change of liver function tests in inconsistent group

Serum ALT, AST, GGT and GLB decreased obviously in inconsistent group ( $P<0.05$ ) or ( $P<0.01$ ), ALB and A/G increased evidently ( $P<0.01$ ), but AKP, TBIL and TP did not change significantly ( $P>0.05$ ), (Table 7).

**Table 7** Comparison of liver function tests between two groups ( $\bar{x}\pm s$ )

Groups	n	TBIL ( $\mu\text{mol/L}$ )	TP (g/L)	ALB (g/L)	GLB (g/L)	A/G
Consistent group	97	18.19±8.51	74.60±6.75	42.34±4.81	32.13±5.18	1.35±0.28
Inconsistent group	16	16.35±6.41	74.31±4.36	46.19±3.61 <sup>b</sup>	28.05±3.47 <sup>b</sup>	1.63±0.26 <sup>b</sup>

<sup>b</sup> $P<0.01$  vs consistent group

Groups	n	ALT(U/L)	AST(U/L)	GGT(U/L)	AKP(U/L)
Consistent group	97	89.28±64.25	66.10±42.30	86.26±70.36	91.65±34.95
Inconsistent group	16	49.31±26.75 <sup>a</sup>	40.83±22.40 <sup>a</sup>	48.99±29.96 <sup>a</sup>	85.25±30.60

<sup>a</sup> $P<0.05$  vs consistent group.

### Results of ultrasonic examination in inconsistent group

Table 8 shows no significant difference in width of main portal vein, splenic vein and thickness of spleen between two groups ( $P>0.05$ ).

**Table 8** Comparison of ultrasonic examination between two groups (cm,  $\bar{x}\pm s$ )

Groups	n	Width of main portal vein	Width of splenic vein	Thickness of spleen
Consistent group	97	1.20±0.13	0.74±0.12	4.02±0.64
Inconsistent group	16	1.23±0.12	0.77±0.13	4.09±0.62

## DISCUSSION

The basic pathological changes of chronic liver disease are inflammation and fibrosis, so they were analysed respectively in pathological diagnosis in recent year. Many semi quantitative score systems, such as Chevallier's criterion, Scheuer's criterion were developed<sup>[31-33]</sup>, so chronic liver disease has been recognized more accurately and profoundly. Staging of liver fibrosis can help us to recognize the development of chronic liver disease. Serum indexes such as HA, PCIII, LN and C-IV which reflect the stage of liver fibrosis have been paid much attention to by many scholars<sup>[34-36]</sup> HA, PCIII, LN and C-IV were mainly produced by hepatic stellate cells<sup>[35,36]</sup>. HA and PCIII were absorbed and degraded by endothelial cells of hepatic sinusoids<sup>[37,38]</sup>. When liver fibrosis takes place, the phenotypes of the membrane of endothelial cells of hepatic sinusoids change, their absorption is blocked, the contents of serum HA, PCIII increase to some degree. LN and C-IV reflected basement membrane transformation and had some relation to portal hypertension<sup>[39,40]</sup>. Many scholars agreed the four serum fibrosis indexes had values in the serodiagnosis of hepatic fibrosis, including the diagnostic value of each serum

fibrosis index and combination of several indexes<sup>[20,29]</sup>. When these indexes were applied to clinical diagnosis, we found some of them were inconsistent with pathological diagnosis. Even with a high stage of hepatic fibrosis, the four serum fibrosis indexes could still be around normal range. So we think it is necessary to find the influencing factors of this phenomenon.

Our results showed the rate of inconsistency between the four serum fibrosis indexes and stage of hepatic fibrosis was 14.16 % in the patients with chronic hepatitis. Table 1 shows the rate of inconsistency of serum HA was 29.21 %, C-IV 31.86 %, PCIII 34.51 % and LN 38.05 %. The rate of consistency between serum HA and stage of hepatic fibrosis was highest, followed by C-IV. This suggests that among the four serum fibrosis indexes, HA is the most ideal index for diagnosing hepatic fibrosis. This was consistent with the results of our previous study on the relationship between serum fibrosis indexes and liver histological changes<sup>[41]</sup>, and was also consistent with other reports in the literature<sup>[42]</sup>. Stage distribution of hepatic fibrosis in inconsistent patients had no significant difference from that of consistent group. This indicates that inconsistency between the four serum fibrosis indexes and stage of hepatic fibrosis has no relationship with the staging. By further study we found inflammation grade of inconsistent patients was lower than that of consistent group. This suggests that the four serum fibrosis indexes are influenced by inflammation grade. In the patients with chronic hepatitis when their stage of hepatic fibrosis is at high level, such as S3 or S4, and inflammation grade is at low level, it is possible that the four serum fibrosis indexes can be inconsistent with stage of hepatic fibrosis. This could be found in patients with advanced stage of schistosomiasis japonica having severe liver fibrosis, but almost no inflammation or decompensation of hepatic function. In addition, it was also suggested that these four serum fibrosis indexes could be lowered by anti-inflammation treatment in patients with chronic hepatitis. As to clinical manifestations, weary degree of inconsistent patients decreased more obviously than that in consistent group. Other profiles had no obvious change. In liver function tests, we found serum ALT, AST, GGT and GLB of inconsistent patients were decreased more obviously, while serum ALB and A/G increased more evidently, serum AKP, TP and TBIL had no significant change. All these suggest that changes of weary degree, serum ALT, AST, GGT, GLB, ALB and A/G were affected by inflammation grade. So they should be taken into account when we assess the diagnostic value of the four serum fibrosis indexes for stage of hepatic fibrosis. At the same time, change of liver function indexes is more sensitive than clinical manifestations. So even without any clinical symptoms, patients should be checked regularly by liver function tests. In clinical practice, width of main portal vein, splenic vein and thickness of the spleen are usually used to determine whether the pressure of main portal vein is increased or not. Table 7 shows they had no significant change, indicating that these patients' condition did not reach the stage of liver cirrhosis.

We conclude that serum fibrosis indexes can only reflect abnormal metabolism of ECM. They are non-specific biochemical markers, when they are used in the diagnosis of hepatic fibrosis, other diseases should be ruled out. They should not be called hepatic fibrosis markers, serum fibrosis indexes should be the appropriate term. Our study indicates the influencing factors include hepatic inflammatory activity, weary degree and some liver function tests. The activity of inflammation is determined by pathological diagnosis of liver biopsy. So in clinical practice, we should put liver function, case history and clinical manifestations all into consideration in assessment of the diagnostic value of these four fibrosis indexes in the staging of hepatic fibrosis. While assessing therapeutic efficacy of anti-fibrosis drugs, we can also not

depend only on these four fibrosis indexes, a comprehensive analysis is necessary. Further studies on new indexes are needed to better understand the pathological changes of liver.

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