P.O.Box 2345, Beijing 100023,China
Fax: +86-10-85381893
E-mail: wjg@wjgnet.com www.wjgnet.com

World J Gastroenterol 2003;9(12):2796-2800
World Journal of Gastroenterology
 ISSN 1007-9327

• CLINICAL RESEARCH •

Relationship between clinical and pathologic findings in patients with chronic liver diseases

Lun-Gen Lu, Min-De Zeng, Yi-Min Mao, Ji-Qiang Li, De-Kai Qiu, Jing-Yuan Fang, Ai-Ping Cao, Mo-Bin Wan, Cheng-Zhong Li, Jun Ye, Xiong Cai, Cheng-Wei Chen, Ji-Yao Wang, Shan-Ming Wu, Jin-Shui Zhu, Xia-Qiu Zhou

Lun-Gen Lu, Min-De Zeng, Yi-Min Mao, Ji-Qiang Li, De-Kai Qiu, Jing-Yuan Fang, Ai-Ping Cao, Shanghai Institute of Digestive Disease, Renji Hospital, Shanghai Second Medical University, Shanghai 200001, China
Mo-Bin Wan, Cheng-Zhong Li, Department of Infectious Diseases, Changhai Hospital, Shanghai 200433, China
Jun Ye, Department of Infectious Diseases, Putuo District Central Hospital, Shanghai 200062, China
Xiong Cai, Department of Infectious Diseases, Changzheng Hospital, Shanghai 200003, China
Cheng-Wei Chen, Shanghai Liver Diseases Research Center of Nanjing Military Command, Shanghai 200233, China
Ji-Yao Wang, Department of Gastroenterology, Zhongshan Hospital, Shanghai 200032, China
Shan-Ming Wu, Shanghai Infectious Disease Hospital, Shanghai 200085, China
Jin-Shui Zhu, Department of Gastroenterology, Shanghai No.6 People' s Hospital, Shanghai 200233, China
Xia-Qiu Zhou, Department of Infectious Diseases, Ruijin Hospital, Shanghai 200025, China
Supported by grants from the Key Project of Shanghai Medical Development Foundation, No.99ZDI001
Correspondence to: Dr. Lun-Gen Lu, MD, Shanghai Institute of Digestive Disease, Renji Hospital, Shanghai Second Medical University, Shanghai 200001, China. lulungen@online.sh.cn
Telephone: +86-21-33070824 **Fax:** +86-21-63364118
Received: 2003-03-28 **Accepted:** 2003-05-11

Abstract

AIM: To explore the relationship between clinical findings of patients with chronic liver diseases and the pathologic grading and staging of liver tissues.

METHODS: The inflammatory activity and fibrosis of consecutive liver biopsies from 200 patients were determined according to the diagnosis criteria of chronic hepatitis in China established in 1995. A comparative analysis was carried out for 200 patients with chronic liver diseases by comparing their clinical manifestations, serum biochemical markers with the grading and staging of liver tissues.

RESULTS: It was revealed that age, index of clinical symptoms and physical signs were obviously relevant to the pathologic grading and staging of liver tissues ($P<0.05$). Blood platelet, red blood cells, aspartate aminotransferase (AST), N-terminal procollagen III (PIII NP) were apparently correlated with the degree of inflammation. PGA (prothrombin time, GGT, apoprotein A1) index, PGAA (PGA+△2-macroglobublin) index, albumin and albumin/globulin were relevant to both inflammation and fibrosis. Hyaluronic acid (HA) was an accurate variable for the severity of hepatic inflammation and fibrosis. The combination of serum markers for fibrosis could increase the diagnostic accuracy. It was notable that viral replication markers were not relevant to the degree of inflammation and fibrosis.

CONCLUSION: There is a good correlation between clinical findings and the pathologic grading and staging of liver tissues, which may give aid to the noninvasive diagnosis of liver fibrosis.

Lu LG, Zeng MD, Mao YM, Li JQ, Qiu DK, Fang JY, Cao AP, Wan MB, Li CZ, Ye J, Cai X, Chen CW, Wang JY, Wu SM, Zhu JS, Zhou XQ. Relationship between clinical and pathologic findings in patients with chronic liver diseases. *World J Gastroenterol* 2003; 9(12): 2796-2800
http://www.wjgnet.com/1007-9327/9/2796.asp

INTRODUCTION

Liver fibrosis is a common sequel to diverse liver injuries. It is characterized by an accumulation of interstitial collagens and other matrix components[1-4]. Chronic liver diseases usually develop into liver cirrhosis through the phase of liver fibrosis[5-8]. In recent years, researchers have been making efforts to study the noninvasive diagnostic methods of liver fibrosis[9-15]. Through a multi-center study, we carried out a comparative analysis of 200 patients with chronic liver diseases by comparing their clinical manifestations, serum biochemical markers with histopathological findings in liver biopsy, in order to appraise the relationship between clinical findings of patients with chronic liver diseases and the grading and staging of liver tissues, and to provide clues and basis for the noninvasive diagnosis of liver fibrosis.

MATERIALS AND METHODS

Patients recruitment

The study was organized and carried out by Shanghai Cooperative Group of Hepatic Fibrosis Project. The Cooperative Group was led by Renji Hospital and Changhai Hospital in Shanghai. Cases provided by the Cooperative Group were as follows: 37 from Changhai Hospital, 36 from Renji hospital, 30 from Putuo District Central Hospital, 22 from Shanghai Hepatic 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 People' s Hospital, 6 from Shanghai Infectious Diseases Hospital, 3 from Ruijin Hospital, 3 from Shanghai No. 9 People' s Hospital, 1 from Shanghai No. 1 People' s Hospital. A total of 200 patients between July and October 1999 were recruited, including 156 male and 44 female patients. The average age of the patients was 34 years (range 15-60 years).

Histological examination

Within 1 week after admission, all the patients received liver puncture biopsy under the guidance of B ultrasound with the 14G quick-cut needle (8-light Company, Japan) or Menghini needle. The length of liver specimens was just 1 cm or longer. The samples were fixed with 10 % formaldehyde, embedded in paraffin and sliced, stained with hematoxylin-eosin, reticular fibers and collagenous fibers. According to the prevention and

treatment program for virus hepatitis set up in 1995[16], all the patients were graded and staged for liver fibrosis and inflammatory activity. Three pathologists read the slides, respectively. The results were statistically analyzed with Kappa test. It was revealed that the consistency of the grading and staging by the pathologists was excellent. All the pathologic diagnoses of liver biopsy were performed by Department of Pathology, Medical College of Fudan University.

Clinical data

General data The general data included age (-25, 25-35, 35-), course of disease (from the time when hepatic symptoms or abnormal laboratory parameters appeared for the first time to the present study) and gender.

Degree of hepatitis The degree of hepatitis was clinically evaluated according to the criteria recommended at the meeting of prevention and treatment of viral hepatitis held in 1995.

Clinical symptoms According to the severity of clinical symptoms such as fatigue, inappetence, swelling, nausea, ache in hepatic region and gingival bleeding, it was scored as 0: no symptom, 1:with one kind of mild symptoms, 2: with one kind of symptoms between mild and severe, 3: with one kind of serious symptoms. It was further divided into 3 grades according to the totaled score: mild: 0-1, moderate: 2-3, severe: $\geqslant$4.

Physical signs According to the degree of hepatomegaly and splenomegaly, it was scored as 0: no hyperplasia (maximal oblique diameter of the right liver <14 cm, thickness of the spleen <4.0 cm); 1: with hepatomegaly (maximal oblique diameter of the right liver >14 cm); 1.5: with mild splenomegaly (thickness of the spleen was between 4-6 cm); 3: with splenomegaly above moderate degree (thickness of the spleen $\geqslant$6.0 cm). It was further divided into 4 grades according to the totaled score: 0: no hyperplasia, 1:hepatomegaly, 1.5: mild splenomegaly, and $\geqslant$2.5: splenomegaly above moderate degree or both splenomegaly and hepatomegaly.

Laboratory parameters

Routine blood test Red blood cells (RBC), white blood cells (WBC) and platelets (PLT) were counted.

Biochemical blood test Total serum bilirubin, AST, ALT, AST/ALT, GGT, albumin (A), albumin (A)/globulin (G), γ-globulin, prothrombin time (PT), apoprotein A1(ApoA1), α2-macroglobulin and α-fetoprotein(AFP) were detected. Among them, PT, GGT and Apo-A1 were integrated as PGA index. PGA and α2-macroglobulin were integrated as PGAA index.

Serum viral markers HBsAg, HBeAg, anti-HBe, anti-HBc, HBV-DNA, anti-HCV and HCV-RNA were detected.

Serum fibrosis parameters Hyaluronic acid (HA), lamilin (LN), N-terminal procollagen III(PIII NP), 7S collagen IV(7S-IV) were included.

Statistical analysis

Analysis of variance was carried out for all the data with SAS software. $P<0.05$ was considered statistically significant.

RESULTS

Relationship between general data and pathological grading and staging of liver tissues

It was revealed that there was a significant difference in inflammatory activity and fibrosis among different age groups (-25, 25-35, 35-) ($P<0.05$). With the increase of age, the degree of fibrosis became more severe. However, there was no significant difference in inflammatory activity and fibrosis between different courses of disease (-1 year, 1-5 years, 5-years) and sexes ($P>0.05$).

Relationship between clinical manifestations and pathological staging of liver fibrosis

The statistical results indicated that there was a significant difference between the severity of hepatitis and inflammatory grading, and fibrosis staging of liver tissues ($P<0.01$) (Table 1).

The symptom accumulation score at different stages of liver fibrosis was significantly different ($P<0.05$). With the increase of score, liver fibrosis tended to be more serious. However, there was no difference between symptom score and inflammatory grading. Statistical analysis of single symptom indicated that only nausea and gingival bleeding had a significant differnce at different stages of liver fibrosis ($P<0.05$ and $P<0.01$, respectively).

Among different groups of inflammatory grading and fibrosis staging, the score of physical signs differed significantly ($P<0.05$), with the increase of score, inflammatory and fibrosis became more serious.

When symptom score and physical signs were combined for a further analysis, all the subjects were divided into 6 groups (Table 1). There were correlations between the inflammatory activity and fibrosis staging, and the differences among different groups were significant ($P<0.01$).

Relationship between biochemical parameters and inflammatory grading and fibrosis staging

The relationship between each single parameter and inflammatory grading and fibrosis staging is shown in Table 2.

From Table 2 we could find that the main biochemical parameters related only to inflammatory grading were RBC, PLT, AST, and PIIINP. With inflammation becoming serious, RBC and PLT tended to decrease, while the level of AST and PIIINP tended to increase. GGT, A, A/G, HA, 7S-IV and AFP were correlated with both inflammation grading and fibrosis staging, with the inflammation and fibrosis becoming more serious. A and A/G tended to decrease, while GGT and AFP tended to increase. There was no significant difference in PT at different stages and grades.

Table 1 Relationship between clinical manifestations and pathological grading and staging of liver tissues

Groups	Symptom score+physical signs	*n*	Inflammatory grading (G) (%)				Fibrosis staging (s) (%)				
			1	2	3	4	0	1	2	3	4
1	0~1+ no hepatomegaly and splenomegaly	15	46.7	40	13.3	0	33.3	26.7	40	0	0
2	0~1+ hepatomegaly and splenomegaly	14	28.6	28.6	28.6	14.3	7.1	35.7	28.6	14.3	14.3
3	~3+no hepatomegaly and splenomegaly	28	42.9	53.6	3.5	0	14.3	50	35.7	0	0
4	2~3 +hepatomegaly and splenomegaly	42	30.9	26.2	28.5	16.7	9.5	23.8	40.5	16.7	9.5
5	$\geqslant$4+ no hepatomegaly and splenomegaly	32	43.7	25	15.6	15.6	12.5	34.3	25	15.6	12.5
6	$\geqslant$4+ hepatomegaly and splenomegaly	69	23.3	21.7	34.8	15.9	2.9	29	29	15.9	23.2
				$P<0.01$					$P<0.01$		

Table 2 Relationship between biochemical parameters and inflammatory grading and fibrosis staging

Parameters	Inflammatory (G) (%)						Fibrosis staging (s) (%)									
	1~2	1~3	1~4	2~3	2~4	3~4	0~1	0~2	0~3	0~4	1~2	1~3	1~4	2~3	2~4	3~4
RBC			b		b	b				a			a		a	a
PLT			b		b	b										
AST		b	b	a	b											
ALT																
AST/ALT																
GGTa	a	b	b	b			b	b	b	b	b	b				
A				b		b				b			b		b	b
A/G				b		b				b			b		b	b
HA	b	b	b	b	b	b			b	b	b	b	b		b	b
LN																
7S-IV		a	b	a	b					a			a		a	
PIIINP			b		b											
AFP	b	b	b	b	b	b		b	b		b	b			b	
PT																

$^{a}P<0.05$, $^{b}P<0.01$.

Table 3 Serologic parameters for diagnosing liver fibrosis and cirrhosis

Parameters	Fibrosis (S0/S1~4)			Cirrhosis (S1~3/S4)		
	Specificity(%)	Sensitivity(%)	Accuracy(%)	Specificity(%)	Sensitivity(%)	Accuracy(%)
HA	94.44	38.26	43.50	90.0	60.0	85.71
PIIINP	16.67	77.71	72.0	78.0	24.0	70.28
LN	55.26	50.29	50.10	54.0	52.0	53.71
7S-IV	50.22	24.67	51.0	93.29	24.0	89.08

Table 4 Serologic parameters for diagnosing liver fibrosis and cirrhosis

Parameters	Fibrosis (S0/S1~4)			Cirrhosis (S1~3/S4)		
	Specificity(%)	Sensitivity(%)	Accuracy(%)	Specificity(%)	Sensitivity(%)	Accuracy(%)
HA+7S-IV	88.89	37.93	42.50	89.93	60.0	85.63
HA+PIIINP	88.89	42.86	47.10	90.0	60.0	85.71
HA+7S-IV+ PIIINP+LN	88.89	47.13	51.04	89.93	64.0	86.21
HA+TIMP	92.86	38.28	43.67	90.27	60.0	86.72
PGA+HA	60.0	60.44	60.40	89.41	66.67	87.91
PGAA+HA	70.0	62.64	63.67	89.41	66.67	87.91
PGA+7S-IV	61.12	50.22	50.31	90.59	33.33	86.80
PGAA+7S-IV	60.0	48.22	50.67	92.94	33.33	89.0

Relationship between PGA, PGAA index and pathological staging and grading

PGA score had a relationship with inflammation and fibrosis ($P<0.01$, $P<0.05$ respectively). Its sensitivity and accuracy for the diagnosis of liver fibrosis were 70.33 % and 67.33 %, respectively, both of which were higher than those for early liver cirrhosis (50.00 % and 57.14 %, respectively). PGAA also correlated with inflammation and fibrosis ($P<0.05$), the sensitivity and accuracy for the diagnosis of liver fibrosis were 63.74 % and 63.37 %, respectively, both of which were higher than those for early liver cirrhosis (33.33 % and 61.64 %, respectively).

Relationship between serum parameters of liver fibrosis and pathological grading and staging

With discriminatory analysis method, we evaluated the significance of assaying single or combined serum parameters of liver fibrosis, in the diagnosis of liver fibrosis and cirrhosis (Tables 3 and 4).

Relationship between viral markers and pathological staging and grading

The statistical results revealed that there was no relationship between viral replication parameters and degrees of inflammation and fibrosis.

DISCUSSION

This study suggested that age was correlated with inflammatory activity, but the course of disease did not. Maybe it is because most of the patients were unaware of the disease, but the course of disease was always calculated from the time when symptoms appeared or people saw a doctor. It could not reflect the course accurately. So it was difficult to discover the relationship between fibrosis severity and the course of the disease[9,13,15].

With the integral method, we scored the severity of symptoms quantitatively, classified the total score, which could reflect the symptom severity comprehensively. The results indicated that there was no correlation between symptom score

and inflammatory activity (P>0.05), but the score correlated with fibrosis stage significantly (P=0.0106). With the symptoms becoming more prominent, fibrosis became more serious. At the same time, it was found that the score of physical signs had a strong relationship with inflammatory activity and fibrosis severity (P<0.05). The higher the physical sign score was, the more serious the inflammatory activity and fibrosis were. When the difference became more significant, the symptoms and signs were combined (P<0.01).

This study indicated that at different fibrosis stage and inflammatory grade of liver tissues, the serum level of HA differed remarkably (P<0.01), which could serve as a sensitive and accurate parameter to identify the severity of hepatic inflammation and fibrosis[17-20]. In addition, HA was a specific and accurate parameter for the diagnosis of early liver cirrhosis, the specificity and accuracy were 90 % and 85 %, respectively. It was also found that PIIINP differed at the different inflammatory grades significantly (P<0.01), but not significantly at different fibrosis stages (P<0.05), indicating that its correlation with inflammatory severity was closer than that with fibrosis. Thus it might be of significance in determining the inflammatory severity.

One conclusion that differs from others is that this study did not agree with the significance of LN in the diagnosis of liver fibrosis. It has been claimed that the diagnostic efficiency would increase when HA was assayed in combination with other parameters, yet it needs to be proved[21-28].

Based on the relationship between a single biochemical parameter and inflammation and fibrosis, we found that PLT, RBC and AST were important in identifying inflammatory severity rather than fibrosis. They differed significantly at grades 1, 2, 3 and 4, so they could help estimate the severity of inflammation. With the inflammation becoming serious, RBC and PLT tended to decrease. Both A and A/G ratio correlated with inflammation and fibrosis, and could be used to identify the severity. Additionally, our study proved that the level of AFP differed significantly at different inflammatory grades and fibrosis stages (P<0.01), indicating that it correlated with inflammation and fibrosis closely, and could be used as an adjuvant parameter[29-32].

PGA (PT, GGT, and ApoA1) and PGAA(PGA+α2-macroglobulin) index were mainly used as liver function indicators put forward in the early 1990' s by some experts to reflect the liver function of patients with alcoholic liver disease, and to screen or diagnose liver cirrhosis[9,33-38].

In recent years, researchers in China have probed into applying PGA index or combining it with other serum parameters to the diagnosis of liver cirrhosis. To some extent, the results of our study are in accordance with the conclusion that both PGAA and PGA correlated with inflammation and fibrosis significantly. However, when the foreign criteria were used, the score of ApoA1 in most normal samples were 4, which were too high, resulting in the increase of total PGA and PGAA scores. Therefore, we considered it abnormal when PGA score was above 6. This difference might be due to the following reasons. First, there was an ethnic difference in the normal range of ApoA1, so it is necessary to set up PGA and PGAA criteria applicable in China. Second, the two parameters were mainly used in alcoholic liver diseases, but most of the patients in our study were viral hepatitis[13-15,17,35,36,39,40].

Our study indicates that, viral replication parameters such as HBeAg and HBV DNA have no correlation with the severity of inflammation and fibrosis. We compared the inflammatory and fibrotic severity in patients with positive markers of hepatitis B only (141 cases) and in those with positive markers of both hepatitis B and C (10 cases), but no statistical difference was found between them. However, as the patients suffering from co-infection of hepatitis B and C were very few in the study, the conclusion needs to be verified by larger sample studies.

REFERENCES

1 **Albanis E**, Friedman SL. Hepatic fibrosis. Pathogenesis and principles of therapy. *Clin Liver Dis* 2001; **5**: 315-334
2 **Brenner DA**, Waterboer T, Choi SK, Lindquist JN, Stefanovic B, Burchardt E, Yamauchi M, Gillan A, Rippe RA. New aspects of hepatic fibrosis. *J Hepatol* 2000; **32**(1Suppl): 32-38
3 **Albanis E**, Safadi R, Friedman SL. Treatment of hepatic fibrosis: almost there. *Curr Gastroenterol Rep* 2003; **5**: 48-56
4 **Rockey DC**. The cell and molecular biology of hepatic fibrogenesis. Clinical and therapeutic implications. *Clin Liver Dis* 2000; **4**: 319-355
5 **Li D**, Friedman SL. Liver fibrogenesis and the role of hepatic stellate cells: new insights and prospects for therapy. *J Gastroenterol Hepatol* 1999; **14**: 618-633
6 **Friedman SL**. Molecular mechanisms of hepatic fibrosis and principles of therapy. *J Gastroenterol* 1997; **32**: 424-430
7 **Musca A**, Paoletti V, De Matteis A, Mammarella A, Labbadia G, Grassi M, Paradiso M. Liver fibrosis: what's the beginning of autonomic deficit? *Scand J Gastroenterol* 2002; **37**: 1235-1236
8 **Dai WJ**, Jiang HC. Advances in gene therapy of liver cirrhosis: a review. *World J Gastroenterol* 2001; **7**: 1-8
9 **Oberti F**, Valsesia E, Pilette C, Rousselet MC, Bedossa P, Aube C, Gallois Y, Rifflet H, Maiga MY, Penneau-Fontbonne D, Cales P. Noninvasive diagnosis of hepatic fibrosis or cirrhosis. *Gastroenterology* 1997; **113**: 1609-1616
10 **Tsutsumi M**, Takase S, Urashima S, Ueshima Y, Kawahara H, Takada A. Serum markers for hepatic fibrosis in alcoholic liver disease: which is the best marker, type III procollagen, type IV collagen, laminin, tissue inhibitor of metalloproteinase, or prolyl hydroxylase? *Alcohol Clin Exp Res* 1996; **20**: 1512-1517
11 **Aube C**, Oberti F, Korali N, Namour MA, Loisel D, Tanguy JY, Valsesia E, Pilette C, Rousselet MC, Bedossa P, Rifflet H, Maiga MY, Penneau-Fontbonne D, Caron C, Cales P. Ultrasonographic diagnosis of hepatic fibrosis or cirrhosis. *J Hepatol* 1999; **30**: 472-478
12 **Zaitoun AM**, Al Mardini H, Awad S, Ukabam S, Makadisi S, Record CO. Quantitative assessment of fibrosis and steatosis in liver biopsies from patients with chronic hepatitis C. *J Clin Pathol* 2001; **54**: 461-465
13 **Fontana RJ**, Lok AS. Noninvasive monitoring of patients with chronic hepatitis C. *Hepatology* 2002; **36**(5 Suppl 1): S57-S64
14 **Thabut D**, Simon M, Myers RP, Messous D, Thibault V, Imbert-Bismut F, Poynard T. Noninvasive prediction of fibrosis in patients with chronic hepatitis C. *Hepatology* 2003; **37**: 1220-1221
15 **Tran A**, Hastier P, Barjoan EM, Demuth N, Pradier C, Saint-Paul MC, Guzman-Granier E, Chevallier P, Tran C, Longo F, Schneider S, Piche T, Hebuterne X, Benzaken S, Rampal P. Non invasive prediction of severe fibrosis in patients with alcoholic liver disease. *Gastroenterol Clin Biol* 2000; **24**: 626-630
16 Prevention and treatment projects of virus hepatitis (tryout). *Zhonghua Neike Zazhi* 1995; **34**: 788-791
17 **Stickel F**, Urbaschek R, Schuppan D, Poeschl G, Oesterling C, Conradt C, McCuskey RS, Simanowski UA, Seitz HK. Serum collagen type VI and XIV and hyaluronic acid as early indicators for altered connective tissue turnover in alcoholic liver disease. *Dig Dis Sci* 2001; **46**: 2025-2032
18 **Guechot J**, Laudat A, Loria A, Serfaty L, Poupon R, Giboudeau J. Diagnostic accuracy of hyaluronan and type III procollagen amino-terminal peptide serum assays as markers of liver fibrosis in chronic viral hepatitis C evaluated by ROC curve analysis. *Clin Chem* 1996; **42**: 558-563
19 **Murawaki Y**, Ikuta Y, Okamoto K, Koda M, Kawasaki H. Diagnostic value of serum markers of connective tissue turnover for predicting histological staging and grading in patients with chronic hepatitis C. *J Gastroenterol* 2001; **36**: 399-406
20 **Pares A**, Deulofeu R, Gimenez A, Caballeria L, Bruguera M, Caballeria J, Ballesta AM, Rodes J. Serum hyaluronate reflects hepatic fibrogenesis in alcoholic liver disease and is useful as a marker of fibrosis. *Hepatology* 1996; **24**: 1399-1403
21 **Zheng M**, Cai WM, Weng HL, Liu RH. ROC curves in evaluation of serum fibrosis indices for hepatic fibrosis. *World J Gastroenterol* 2002; **8**: 1073-1076
22 **Zheng M**, Cai W, Weng H, Liu R. Determination of serum fibrosis indexes in patients with chronic hepatitis and its significance. *Chin Med J* 2003; **116**: 346-349

23 **Shahin M**, Schuppan D, Waldherr R, Risteli J, Risteli L, Savolainen ER, Oesterling C, Abdel Rahman HM, el Sahly AM, Abdel Razek SM. Serum procollagen peptides and collagen type VI for the assessment of activity and degree of hepatic fibrosis in schistosomiasis and alcoholic liver disease. *Hepatologl* 1992; **15**: 637-644

24 **Ramadori G**, Zohrens G, Manns M, Rieder H, Dienes HP, Hess G, Meyer KH, Buschenfelde Z. Serum hyaluronate and type III procollagen aminoterminal propeptide concentration in chronic liver disease. Relationship to cirrhosis and disease activity. *Eur J Clin Invest* 1991; **21**: 323-330

25 **Hirayama C**, Suzuki H, Takada A, Fujisawa K, Tanikawa K, Igarashi S. Serum type IV collagen in various liver diseases in comparison with serum 7S collagen, laminin, and type III procollagen peptide. *J Gastroenterol* 1996; **31**: 242-248

26 **Fabris C**, Falleti E, Federico E, Toniutto P, Pirisi M. A comparison of four serum markers of fibrosis in the diagnosis of cirrhosis. *Ann Clin Biochem* 1997; **34**(Pt 2): 151-155

27 **Walsh KM**, Fletcher A, MacSween RN, Morris AJ. Comparison of assays for N-amino terminal propeptide of type III procollagen in chronic hepatitis C by using receiver operating characteristic analysis. *Eur J Gastroenterol Hepatol* 1999; **11**: 827-831

28 **Castera L**, Hartmann DJ, Chapel F, Guettier C, Mall F, Lons T, Richardet JP, Grimbert S, Morassi O, Beaugrand M, Trinchet JC. Serum laminin and type IV collagen are accurate markers of histologically severe alcoholic hepatitis in patients with cirrhosis. *J Hepatol* 2000; **32**: 412-418

29 **Lin DY**, Chu CM, Sheen IS, Liaw YF. Serum carboxy terminal propeptide of type I procollagen to amino terminal propeptide of type III procollagen ratio is a better indicator than each single propeptide and 7S domain type IV collagen for progressive fibrogenesis in chronic viral liver diseases. *Dig Dis Sci* 1995; **40**: 21-27

30 **Myers RP**, De Torres M, Imbert-Bismut F, Ratziu V, Charlotte F, Poynard T. Biochemical markers of fibrosis in patients with chronic hepatitis C: a comparison with prothrombin time, platelet count, and age-platelet index. *Dig Dis Sci* 2003; **48**: 146-153

31 **Imbert-Bismut F**, Ratziu V, Pieroni L, Charlotte F, Benhamou Y, Poynard T. Biochemical markers of liver fibrosis in patients with hepatitis C virus infection: a prospective study. *Lancet* 2001; **357**: 1069-1075

32 **Naveau S**, Montembault S, Balian A, Giraud V, Aubert A, Abella A, Capron F, Chaput JC. Biological diagnosis of the type of liver disease in alcoholic patients with abnormal liver function tests. *Gastroenterol Clin Biol* 1999; **23**: 1215-1224

33 **Myers RP**, Ratziu V, Imbert-Bismut F, Charlotte F, Poynard T. Biochemical markers of liver fibrosis: a comparison with historical features in patients with chronic hepatitis C. *Am J Gastroenterol* 2002; **97**: 2419-2425

34 **Pilette C**, Rousselet MC, Bedossa P, Chappard D, Oberti F, Rifflet H, Maiga MY, Gallois Y, Cales P. Histopathological evaluation of liver fibrosis: quantitative image analysis vs semi-quantitative scores. Comparison with serum markers. *J Hepatol* 1998; **28**: 439-446

35 **Naveau S**, Poynard T, Benattar C, Bedossa P, Chaput JC. Alpha-2-macroglobulin and hepatic fibrosis. Diagnostic interest. *Dig Dis Sci* 1994; **39**: 2426-2432

36 **Jiang JJ**, Salvucci M, Thepot V, Pol S, Ekindjian OG, Nalpas B. PGA score in diagnosis of alcoholic fibrosis. *Lancet* 1994; **343**: 803

37 **Teare JP**, Sherman D, Greenfield SM, Simpson J, Bray G, Catterall AP, Murray-Lyon IM, Peters TJ, Williams R, Thompson RP. Comparison of serum procollagen III peptide concentrations and PGA index for assessment of hepatic fibrosis. *Lancet* 1993; **342**: 895-898

38 **Croquet V**, Vuillemin E, Ternisien C, Pilette C, Oberti F, Gallois Y, Trossaert M, Rousselet MC, Chappard D, Cales P. Prothrombin index is an indirect marker of severe liver fibrosis. *Eur J Gastroenterol Hepatol* 2002; **14**: 1133-1141

39 **Cadranel JF**, Mathurin P. Prothrombin index decrease: a useful and reliable marker of extensive fibrosis? *Eur J Gastroenterol Hepatol* 2002; **14**: 1057-1059

40 **Lu LG**, Zeng MD, Wan MB, Li CZ, Mao YM, Li JQ, Qiu DK, Cao AP, Ye J, Cai X, Chen CW, Wang JY, Wu SM, Zhu JS, Zhou XQ. Grading and staging of hepatic fibrosis, and its relationship with noninvasive diagnostic parameters. *World J Gastroenterol* 2003; **9**: 2574-2578

Edited by Zhu LH and Wang XL