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Preoperative evaluation of the degree of liver fibrosis based on matter-element analysis using serological indicators in patients with hepatocellular carcinoma

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Summary **Evaluation of the degree of liver fibrosis is an important basis for the clinical diagnosis and treatment of patients with hepatocellular carcinoma (HCC). It is meaningful to make a preoperative evaluation with non-invasive methods. In the current study, 12 commonly used preoperative serological indicators from 161 HCC patients with different degree of liver fibrosis were collected retrospectively, and 8 of the indicators (ALB, PA, TBil, INR, AST, GGT, ALP, and PT) were ultimately used in matter-element analysis to create a formula. The relationship between those results and the histological sub-classification of the Laennec liver fibrosis scoring system was analyzed. The calculated value of R from this formula will indicate the differing degree of liver fibrosis in a patient: *i*) the value of $0.802 \leq R < 1$ indicates the early stage of liver cirrhosis, which corresponds to Laennec stages 0-3; *ii*) the value of $0.752 \leq R < 0.802$ indicates the mild stage of liver cirrhosis, which corresponds to Laennec stage 4A; *iii*) the value of $0.698 \leq R < 0.752$ indicates the moderate stage of liver cirrhosis, which corresponds to Laennec stage 4B; and *iv*) the value of $0.444 \leq R < 0.698$ indicates the severe stage of liver cirrhosis, which corresponds to Laennec stage 4C. The hope is that this formula for preoperative evaluation of the degree of liver fibrosis using non-invasive methods would be useful in the clinical diagnosis and treatment of patients with HCC in the future.**

Keywords: Liver cirrhosis, Laennec system, matter-element analysis

1. Introduction

Cirrhosis is defined as regenerative nodules surrounded by extensive fibrosis (*1*). Liver fibrosis is a pathological process of abnormal proliferation of connective tissues caused by various pathogenic factors, in which excessive extracellular matrix proteins accumulate in the liver. Among the various causes of liver fibrosis, viral hepatitis, alcoholic liver, fatty liver, and autoimmune diseases are the most common in clinical settings (*2-4*). Without proper treatment, liver fibrosis can eventually develop into cirrhosis and hepatocellular carcinoma (HCC) with the progression of the disease (*5-7*). Therefore, evaluation of the degree of liver fibrosis is an important basis for the clinical diagnosis and treatment of patients with the disease.

For semi-quantitative estimation of fibrosis, the Laennec system (Table 1) that is based on histological parameters of fibrous septa according to their width and number has been proposed. The Laennec system subdivides the most severe stage of fibrosis (F4) into 4A, 4B, and 4C in order to acknowledge the varying severity of cirrhosis (*8-10*). However, the Laennec system is based on histological parameters of fibrous septa. Preoperative evaluation of the degree of liver fibrosis based on a simple and effective non-invasive method would prove beneficial.

The search for disease-related biomarkers in plasma has made rapid progress over the past few years, and the

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significance of biomarkers in diagnosis of disease has been widely demonstrated (*11*). Determining a useful method of evaluating the degree of liver fibrosis with serological biomarkers would be of great significance.

Various scoring formulae have been devised to evaluate HCC with serological biomarkers (*12*). A previous study by the current authors found that a scoring formula for liver injury (SFLI) was useful in the assessment of liver damage (*13*). SFLI was based on matter-element analysis. In the current study, matter-element analysis was used to create a formula based on serological indicators to facilitate preoperative evaluation of the degree of liver fibrosis in patients with HCC. The relationship between those results and the histological sub-classification of the Laennec system was analyzed.

2. Materials and Methods

2.1. *Study population*

From June 2010 to June 2015, 362 patients with HCC were treated in the Department of Liver Surgery of Yichang Central People's Hospital; 300 of those patients were diagnosed with different degrees of liver fibrosis. Patients under 30 years of age or over 70 years of age were excluded, patients with active hepatitis, patients using immunosuppressive or antiviral drugs, and patients with HIV, HCV, decompensation of the liver, alcoholic hepatitis, or an autoimmune disease were also excluded. Ultimately, 161 patients were enrolled in this study.

Data such as the patient's medical history, results of physical examinations, results of B-mode ultrasound, computed tomography (CT) scans, magnetic resonance imaging (MRI) scans, biochemistry, and results of post-operative pathology were retrospectively collected for all 161 patients. Paraffin-embedded specimens were obtained from Yichang Central People's Hospital for research purposes. This study was approved by the Ethics Committee of the First Clinical Medicine College Hospital of China Three Gorges University.

2.2. *Collection of data on serological indicators*

Data on the following 12 commonly used serological indicators were collected in this study: serum albumin (ALB), prealbumin (PA), serum total bilirubin (TBiL), the international normalized ratio (INR), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), prothrombin time (PT), serum creatinine (SCr), alanine aminotransferase (ALT), activated partial thromboplastin time (APTT), and thrombin time (TT). The serological indicators were collected in the first morning when the patients visited the doctors.

The normal values for these indicators were: ALB, 35-55 g/L; PA, 100-400 mg/L; TBiL, 2.04-20.4 μmol/L; INR, 0.8-1.5; AST, 0-40 U/L; GGT, 0-54 U/L; ALP, 39-117 U/L; PT, 11-13s; SCr, 70-106 μmol/L; ALT, 0-40 U/L; APTT, 28-41s; TT, 13-18s.

In order to comply with the statistical principles of matter-element analysis, the 161 patients were divided into 8 groups by age: 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, and 65-69.

2.3. *Pathological grading according to the Laennec system*

After they were embedded in paraffin, 161 liver tissue specimens were cut into sections. Masson trichrome staining was performed as usual. All pathological sections were graded independently by two pathologists in this Hospital, the samples with the same result were selected and graded according to the Laennec liver fibrosis scoring system (*9,14*).

In accordance with the histological sub-classification of the Laennec system (Table 1), liver fibrosis in 161 patients was divided into 7 degrees from mild to severe. Liver fibrosis was grades 0-3 (the early stage of liver cirrhosis) in 15 patients, grade 4A (the mild stage of liver cirrhosis) in 42, grade 4B (the moderate stage of liver cirrhosis) in 55, and grade 4C (the severe stage of liver cirrhosis) in 49.

2.4. *Creation of a scoring formula using matter-element analysis*

In the process of creating a mathematical formula to score liver fibrosis, matter-element analysis was mainly used to solve for the weight of each detection index. The R value was calculated according to the fibrosis scoring formula. The method used was as follows:

(1) The age range of patients in the experiment was considered to be Tm, each measurement indicator was considered to be Cn, and the obtained data were considered to be Xji (j=1,2,…,m; i=1,2,…, n). The following matter elements were successfully constructed:

$$R_{mn}=\begin{vmatrix} & T_1 & T_2 & \cdots & T_m \\ C_1 & X_{11} & X_{21} & \cdots & X_{m1} \\ C_2 & X_{12} & X_{22} & \cdots & X_{m2} \\ \cdots & \cdots & \cdots & \cdots & \cdots \\ C_n & X_{1n} & X_{2n} & \cdots & X_{mn} \end{vmatrix}$$

(2) Determination of the membership degree (U): in order to obtain the weight of each measurement indicator in the fibrosis scoring formula, a measurement standard should be determined. This standard was determined using membership degree (U), which was

determined using the following method:

smaller measurement values indicated better results:

$$U_{ji}=\frac{\max X_{ji}-X_{ji}}{\max X_{ji}-\min X_{ji}}$$

greater measurement values indicated better results:

$$U_{ji}=\frac{X_{ji}-\min X_{ji}}{\max X_{ji}-\min X_{ji}}$$

where maxXji and minXji, represent the corresponding maximum and minimum values of Xji in each age group respectively.

(3) Conversion of the membership degree into relevance: the relevance conversion is the conversion between the degree of membership and the correlation coefficient. Since the correlation coefficient (ξ) is equivalent to the membership function, the correlation coefficient ξji can be determined from the membership coefficient Uji, namely: ξji=Uji(j=1,2,…,m; i=1,2,…, n).

(4) Establishment of the fuzzy matter element:

$$R_\xi=\begin{vmatrix} & P_1 & P_2 & \cdots & P_m \\ C_1 & \xi_{11} & \xi_{21} & \cdots & \xi_{m1} \\ C_2 & \xi_{12} & \xi_{22} & \cdots & \xi_{m2} \\ \cdots & \cdots & \cdots & \cdots & \cdots \\ C_n & \xi_{1n} & \xi_{2n} & \cdots & \xi_{mn} \end{vmatrix}$$

(5) Solving the weight for each indicator in the fibrosis scoring formula

Wj represents the weight for each indicator:

$$W_j=\begin{vmatrix} m & m & n \\ \sum \xi_{ji}/ & \sum & \sum \xi_{ji} \\ j=1 & j=1 & i=1 \end{vmatrix}$$

And

$$R_w=\begin{vmatrix} & C_1 & C_2 & \cdots & C_n \\ W_j & W_1 & W_2 & \cdots & W_n \end{vmatrix}$$

2.5. *Statistical analysis*

All of the determined indicators were used to construct a table, and Excel and the statistical software SPSS 18.0 were used to perform statistical analysis. The results are expressed as the mean + SD (± S). LSD and SNK were used when homogeneity of variance was present in group pair-wise comparisons, or Tamhane's T2 was more appropriate. ALB, PA, TBiL, SCr, INR, ALT, AST, gamma-GT, ALP, PT, and APTT were compared with their corresponding normal values. An Excel function was used to perform a *t*-test and the software SPSS18.0 was used to perform a *t*-test and analysis of variance. $p < 0.05$ served as the level of significance, and $p < 0.01$ indicated a significant difference.

The one-way analysis of variance was performed if the obtained data followed a normal distribution. Otherwise, the Kruskal Wallis test was used instead to analyze the correlation. In addition, Spearman rank correlation analysis was used in the correlation of all indexes and pathological diagnosis of the stage of liver fibrosis.

3. Results

3.1. *Screening on preoperative serological indicators*

Serological indicators and the stage of fibrosis were analyzed in the 161 patients according to the Laennec liver fibrosis scoring system (Table 1). Correlation analysis indicated that 11 of the 12 indicators were correlated with the Laennec liver fibrosis scoring system (Table 2), although some of the correlations were relatively weak (rs < 0.4). To optimize indicator selection, APTT and TT were excluded from analysis since these two indicators had a very low correlation. SCr was also excluded because its p value was greater than 0.05. Moreover, ALT was excluded since it belongs to the same system as AST, and AST is reported to be more strongly correlated with liver fibrosis than ALT (*15*).

Ultimately, 8 indicators − ALB, PA, TBiL, INR, AST, GGT, ALP, and PT − were selected for use in creating a formula using matter-element analysis.

3.2. *Creation of the liver fibrosis formula*

A database of the 8 preoperative serological indicators was created, and statistical analysis was performed using the statistical software SPSS18.0. Patients were divided into 8 age groups in increments of 5 years. Comparison between groups was performed with the range of reference values and the overall mean according to the t-test. A result greater than the upper limit or less than the lower limit was considered significant, with a test level (α) of 0.05. Indicators resulting in significant differences were incorporated into the element of matter-element analysis, and the liver fibrosis formula was then created.

Liver fibrosis in the 161 patients was classified as grades 0, 1, 2, 3, 4A, 4B, and 4C. The 8 preoperative

Table 1. The Laennec liver fibrosis scoring system in liver biopsies*

Stage	Name	Septa (thickness and number)	Criteria	Score
0	No definite fibrosis	+/−	No definite fibrosis.	0
1	Minimal fibrosis	+	No septa or rare thin septum; may have portal expansion or mild sinusoidal fibrosis.	1
2	Mild fibrosis	++	Occasional thin septa; may have portal expansion or mild sinusoidal fibrosis.	2
3	Moderate fibrosis	+++	Moderate thin septa; up to incomplete cirrhosis.	3
4A	Cirrhosis, mild, definite, or probable	++++	Marked septation with rounded contours or visible nodules; Most septa are thin (one broad septum allowed).	4
4B	Moderate cirrhosis	+++++	At least two broad septa, but no very broad septa and less than half of biopsy length composed of minute nodules	5
4C	Severe cirrhosis	++++++	At least one very broad septum or more than half of biopsy length composed of minute nodules (micronodular cirrhosis)	6

*Histological sub-classification according to the Laennec system based on references (*9,14*).

Table 2. Spearman correlation analysis between serum markers and the Laennec liver fibrosis scoring system

Serum markers	r_s	*p* value
ALB (g/L)	- 0.213	0.003
PA (mg/L)	- 0.344	0.000
TBiL (μmol/L)	0.232	0.041
INR	0.128	0.000
AST (U/L)	0.357	0.000
GGT (U/L)	0.311	0.002
ALP (g/L)	0.212	0.004
PT (s)	0.198	0.048
SCr (μmol/L)	0.358	0.435
ALT (U/L)	0.214	0.000
APTT (s)	0.111	0.025
TT (s)	0.125	0.032

AlB, albumin; PA, prealbumin; TBil, total bilirubin; INR, international normalized ratio; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; ALP, alkaline phosphatase; PT, prothrombin time; SCr, serum creatinine; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; TT, thrombin time.
*$p < 0.05$ or **$p < 0.01$ *vs*. normal value.

serological indicators from those 161 patients were substituted into the liver fibrosis scoring formula to calculate the R value. The R value was then compared to the Laennec liver fibrosis scoring system, and a grading standard for the liver fibrosis scoring formula was obtained.

Using matter-element analysis, the following liver fibrosis formula was created with the 8 preoperative serological indicators:

$$R = a \times \frac{ALB - 22.17}{49.56} + b \times \frac{PA - 4.7}{202.6} + c \times \frac{117.9 - TBiL}{113.98} + d \times \frac{2.36 - INR}{1.56} + e \times \frac{304 - AST}{289} + f \times \frac{774 - GGT}{759} + g \times \frac{646 - ALP}{594} + h \times \frac{28.5 - PT}{17.7}$$

In this formula, ALB, PA, TBiL, INR, AST, GGT, ALP, and PT represent the clinical levels of these 8 indicators. The weights are represented by a-h, and they were determined using matter-element analysis. From a-h, the determined values were 0.0739, 0.1694, 0.0519, 0.0029, 0.1467, 0.1663, 0.3527, and 0.0362. The pre-set data are from the 161 patients; 22.17 and 4.7 are the minimum detected values for ALB and PA, respectively, whereas 117.9, 2.36, 304, 774, 646, and 28.5 represent the maximum clinical values for TBiL, INR, AST, GGT, ALP, and PT, respectively (Table 3). The values of the denominators in the formula were equal to the maximum values minus the minimum values. The value of R calculated using this formula will indicate the patient's stage of liver fibrosis.

3.3. *Degree of liver fibrosis according to the R value*

Based on the R value according to the above formula, different degrees of liver fibrosis were identified: *i*) the value of $0.802 \leq R < 1$ indicates the early stage of liver cirrhosis, which corresponds to Laennec stages 0-3; *ii*) the value of $0.752 \leq R < 0.802$ indicates the mild stage of liver cirrhosis, which corresponds to Laennec stage 4A; *iii*) the value of $0.698 \leq R < 0.752$ indicates the moderate stage of liver cirrhosis, which corresponds to Laennec stage 4B; and *iv*) the value of $0.444 \leq R < 0.698$ indicates the severe stage of liver cirrhosis, which corresponds to Laennec stage 4C. In addition, R = 1 indicates normal liver tissue, representing well liver function.

4. Discussion

Liver cirrhosis is a disease that affects a massive number

Table 3. Test results of liver fibrosis indicators for different age groups

Age (years)	*n*	ALB (g/L)	PA (mg/L)	Tbil (μmol/L)	INR	AST (U/L)	GGT (U/L)	ALP (g/L)	PT (s)
Normal values	161	35 - 55	100 - 400	2.04 - 20.4	0.8 - 1.5	0 - 40	0 - 54	39 - 117	11 - 13
30 - 34	6	34.82 ± 6.41	124.61 ± 72.01	38.69 ± 17.57	1.28 ± 0.19**	70.83 ± 71.39**	94.28 ± 115.83*	122.43 ± 91.34	14.12 ± 2.45**
35 - 39	23	35.24 ± 5.61	133.48 ± 67.32*	35.82 ± 72.29**	1.23 ± 0.17**	71.06 ± 64.01**	96.78 ± 112.45**	121.43 ± 67.69	13.65 ± 2.17**
40 - 44	27	35.16 ± 5.69	132.50 ± 71.65**	31.73 ± 42.65**	1.17 ± 0.16**	70.21 ± 71.44**	134.32 ± 120.35**	132.56 ± 98.87**	13.17 ± 2.63
45 - 49	38	35.89 ± 5.42*	129.37 ± 68.51*	28.32 ± 62.21**	1.16 ± 0.15**	71.81 ± 67.79**	125.44 ± 134.39**	137.23 ± 89.19	13.10 ± 2.82
50 - 54	26	33.96 ± 5.59**	119.54 ± 81.20**	26.89 ± 56.43*	1.19 ± 0.14**	69.36 ± 81.33**	125.21 ± 113.64**	121.34 ± 86.23	13.86 ± 2.21**
55 - 59	21	33.51 ± 7.07**	121.46 ± 59.26**	27.05 ± 82.26*	1.15 ± 0.16**	67.60 ± 43.12*	123.89 ± 132.24**	128.54 ± 101.37	14.02 ± 2.14
60 - 64	11	34.21 ± 6.37**	114.59 ± 87.31**	32.49 ± 55.73	1.12 ± 0.19**	72.97 ± 69.45**	116.14 ± 125.38*	129.32 ± 83.46	13.11 ± 2.76
65 - 69	9	33.42 ± 5.81	125.48 ± 68.24*	38.45 ± 72.29**	1.10 ± 0.13**	68.38 ± 75.24**	114.54 ± 115.04**	135.12 ± 99.87	12.48 ± 2.38

AlB, albumin; PA, prealbumin; TBil, total bilirubin; INR, international normalized ratio; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; ALP, alkaline phosphatase; PT, prothrombin time. *$p < 0.05$ or **$p < 0.01$ *vs.* normal value.

of patients worldwide. As this disease progresses, it is more difficult to cure clinically. Many cases of liver fibrosis develop into liver cirrhosis and even liver cancer due to delayed diagnosis. Therefore, liver cirrhosis needs to be properly diagnosed and staged.

A liver biopsy is still considered to be the "gold standard" for evaluating the severity of liver cirrhosis (*16,17*). For example, the pathological grading of fibrosis in China is divided into four stages according to the prevention and treatment of viral hepatitis, and liver cirrhosis is the highest level. Nonetheless, long-term clinical practice has revealed that conditions differ in different patients with liver cirrhosis, challenging classification based on a liver biopsy. The traumatic consequences of liver biopsy are discouraging to most patients and could result in accidental deaths in extreme cases.

To overcome the aforementioned problems with liver biopsy, some studies have developed mathematical methods to evaluate liver function. The semi-quantitative Child-Pugh score is widely used to evaluate liver function, and it takes into account both clinical and biochemical parameters in patients with liver cirrhosis (*18*). Recent studies have also found that the MELD score was better at assessing the severity and prognosis of end-stage liver diseases than the Child-Pugh score (*19-21*).

Another important factor for evaluating the clinical treatment of liver cirrhosis is the stage. The Laennec liver fibrosis scoring system is widely used in clinical settings, and it divides liver cirrhosis into several levels according to the thickness of the fibrous septa and regenerative nodules. However, the Laennec system is not flawless. In some cases, stage 4C liver fibrosis was expected to improve to stage 4A after anti-fibrosis therapy, but the grading system could not accurately identify that improvement, which could lead to false conclusions. Therefore, more accurate grading methods need to be devised to classify liver cirrhosis in more detail (*22-25*).

The liver has a variety of metabolic functions, and it also has a strong capacity for storage, compensation, and regeneration. When the liver is damaged to a certain extent, the amount of some substances synthesized and secreted by the liver or the activity of some enzymes in serum will be abnormal. Detection of these indicators can indicate liver damage and pathological changes. SFLI was obtained using matter-element analysis, and studies have indicated that its results agree with the Child-Pugh classification and also provide a more objective basis for early diagnosis, grading of liver function, and determination of the development of liver cirrhosis and its prognosis (*12,13*). Liver fibrosis is a process of abnormal proliferation of connective tissue in the liver caused by various pathogenic factors. All liver injury and repair and healing processes cause fibrosis, which is accompanied by the expression or

inhibition of fibrosis-related proteins. Therefore, the current study used matter-element analysis to create a formula based on serological indicators in order to facilitate preoperative evaluation of the degree of liver fibrosis in patients with HCC. This study also analyzed the relationship between the results of that formula and histological sub-classification of the Laennec system. The hope is to devise a simple and universally acceptable method that can indicate the degree of liver fibrosis in patients with HCC in a short of time following a clinical examination.

In conclusion, 8 preoperative serological indicators (ALB, PA, TBil, INR, AST, GGT, ALP, and PT) were retrospectively determined in 161 patients with HCC and different degrees of liver fibrosis to establish a formula using matter-element analysis. The hope is that such a formula for preoperative evaluation of the degree of liver fibrosis using non-invasive methods would be useful in the clinical diagnosis and treatment of patients with HCC in the future.

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