EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 5
Issue: 8
50-53
Year: 2018

PROGNOSTIC MARKER OF LIVER FIBROSIS IN PATIENTS WITH CHRONIC VIRAL HEPATITIS B AND D.

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Article Received on 26/05/2018 **Article Revised on 14/06/2018** **Article Accepted on 05/07/2018**

ABSTRACT
The diagnostic significance of WFA+-M2BP was assessed for establishing the degree of liver fibrosis and predicting the risk of developing liver chirrosis. We examined 41 naive patients with chronic viral hepatitis and viral liver chirrosis. The results of the conducted studies indicate that the serum LF marker WFA+-M2BP is useful in chronic viral hepatitis for assessing the degree of liver damage.

KEYWORDS: chronic hepatitis B, D, HBV, HDV, liver fibrosis, liver cirrhosis, WFA+-M2BP, elastography.

BACKGROUND

Serological markers of liver fibrosis (LF) are divided into indirect, indicating a violation of liver function with severe fibrosis and liver cirrhosis (LC) and direct. Indirect serological markers of LF include routine laboratory tests, which make it possible to assess the presence of LF. The possibilities of direct serological markers of fibrosis are broader, they reflect the dynamics of the number of fibrous fibers and their components at all stages of fibrosis and the presence of LC. Direct indicators of the transformation of the structure of the liver are serum markers of LF.

Direct and affordable methods for evaluating LF include ultrasonic elastography using the apparatus. Restriction of the application of this method is ascites, excessive fatty tissue, diseases of the biliary tract, including cholelithiasis. Thus, it is simply impossible for some patients to carry out this study. Low sensitivity (66,0%) of elastography at the stages of LF F0-F1 dictates the need for using other tests to determine the degree of LF.[1]

AIM OF STUDY: To assess the diagnostic significance of the WFA+-M2BP definition for determining the degree of LF and the possibility of using this serum marker to predict the risk of developing the cerebral cortex and to identify functional liver reserves.

MATERIALS AND METHODS

Etiological diagnosis was established based on the results of an enzyme immunoassay (ELISA). For detection of HBsAg, antibodies to HDV in the serum was used diagnostic kits «Diagnostic systems, Nizhny Novgorod, Russia». Polymerase chain reaction (PCR) was used to confirm the diagnosis with using kits «AmpliSens HBV-FL and HDV-FL, Russia» for detection of DNA HBV and RNA HDV, respectively.

M2BP immunoprecipitation from serum samples was used to assess the severity of LF and the ability and to predict the outcomes of hepatitis B and D using an automated protein purification system (ED-01, GP BioSciences Ltd., Yokohama, Japan).

Puncture liver biopsy used to determine the histological evaluation of the degree of activity of the process in the liver.

Ultrasound examination of the liver, gall bladder and spleen was carried out using the apparatus of Haiying production of China.

The degree of fibrosis was assessed with the FibroScan 502 S01462 manufactured in France.

RESULTS

Serum values of WFA+-M2BP were evaluated in 41 naive patients with chronic viral hepatitis and viral LC. The diagnostic accuracy of WFA+-M2BP was compared with various fibrosis markers, such as puncture biopsy and liver elastography. Diagnoses are focused on the parameters of the histological examination. The study included 9 patients with chronic hepatitis B (CHB), 15 patients with CHB+D, 11 people with CHB+D with signs of transition to LC, and 6 patients with LC of HBV and HDV etiology. Analysis of the obtained data showed that at CHB levels of WFA+-M2BP were represented by values from 0.33 to 4.13 and only one patient had indicators of 10.6. The average values were 1.14±0.2.

Clinical diagnoses coincided with histological diagnoses in practically all patients and corresponded to low values of WFA+-M2BP. According to the parameters of the liver elastography the degree of fibrosis corresponded to F0-F3 on average 10.6±2.1 kPa. The results of histological studies corresponded to the liver elastography data in 6 out of 9 cases. When comparing the results of histological analysis with WFA+ -M2BP indices, it was revealed that, only one patient had high rates with a histological diagnosis of chronic hepatitis of minimal activity, with fibrosis areas, and WFA+-M2BP had high levels. With further monitoring this patient showed symptoms of LC in 1 year.

Serum values of WFA+-M2BP were assessed in 15 naive patients with CHB with Delta agent (B+D). The average serum concentration of WFA+-M2BP was 1.60±0.23, WFA+-M2BP fluctuations were 0.47 to 3.09, and only one patient had this indicator at 5.55. In this group histological diagnosis in 7 (46.7%) patients did not coincide with clinical diagnosis. There was a reassessment of the patient's condition; the LC was diagnosed more often. Clinicians established LC, while histological examination showed chronic moderate hepatitis. The average values of the degree of LF according to the data of the liver elastography were 7.8±2.4 kPa. The parameters of the liver elastography corresponded to fibrosis from F0 to F3. Histological indices did not correspond to the data of elastography in 6 (40%) patients. The WFA+-M2BP measures averaged 1.6±0.23.

In terms of diagnosis it was difficult for clinicians to diagnose the condition of a patient with a histological diagnosis of chronic hepatitis with a transition to LC or starting LC. In 5 out of 11 patients in this group, clinical diagnoses did not match the results of histological studies, in this case underestimation of the condition occurred. In 3 cases out of 11, the liver fibroscan data did not coincide with the histological indices and indicated the F3 LF. Against this backdrop, WFA+-M2BP had the best result. The average indices of WFA+-M2BP in this group corresponded to 3.22±0.5, although they had a large range of oscillations from 0.35 to 6.86 and 12.5 in one patient. Low values of WFA+-M2BP were observed in 2 patients with CHB+D with signs of transition to LC, that is in 18.2% of cases, WFA+-M2BP values in this group did not provide an opportunity to correctly assess the patient's condition and the depth of liver damage. In 6 patients WFA+-M2BP data did not coincide with liver elastography. This means that the serum markers of LF can be used for borderline states of the transition of chronic hepatitis to LC, since it is clinically difficult to assess the patient's condition in 45.4% of cases.

Thus, in case of CHB+D it is necessary to use serum markers to determine the degree of LF, since the clinical picture does not correspond to the severity of liver damage. In almost half the cases, the clinical diagnosis does not correspond to the histological diagnosis. Low scores of WFA+-M2BP can help in assessing the patient's condition. There was no significant difference between mean values of WFA+-M2BP in patients with CHB and viral hepatitis B+D. High values of WFA+-M2BP for low-activity CHB can serve as a predictive marker for the progression of the process. With chronic hepatitis B+D it is difficult to assess the true state of the patient, as the clinical picture can be expressed even with minor changes in the liver. Low values of WFA+-M2BP can help in a certain state of the patient. The parameters of elastography also did not determine the true state of the disease in 27.2% of cases. One out of six patients had low M2BP values of 1.41 in a group of people with LC of Child-Pugh classes A and B, the remaining five patients had serum markers ranged from 3.33 to 14.73, an average of 6.62±0.5. High liver elastography was observed, which amounted to 20.8±7.0 kPa, which corresponded to a F3-F4 LF. Clinical diagnoses in 5 out of 6 patients coincided with histological and in 5 of 6 patients with WFA+-M2BP. This indicates that in the group of patients with LC it is not advisable to use this marker as a diagnostic criterion for LC as the percentage of coincidence of clinical diagnoses with histological and elastography of the liver was high (Table).

Table: Frequency of mismatch of diagnoses in different groups of patients

Not a coincidence of diagnoses	CHB (n=9)	CHD (n=15)	CHB with transition to the LC (n=11)	LC (n=6)
M2BP with histology	0	2 (13,3%)	2 (18,2%)	1 (16,7%)
Clinical and histological diagnoses	0	7 (46,7%)	5 (45,4%)	1 (16,7%)
Elastography of the liver with a histological diagnosis	3 (33,3%)	6 (40,0%)	3 (27,2%)	1(16,7%)

In CHB histological diagnoses coincided with data of M2BP. In CHB with Delta agent, M2BP values did not correspond to a histological diagnosis in 13.3% of the patients examined. In 46.7% of cases histological diagnoses did not coincide with clinical ones. In CHB with the transition to LC, the M2BP indices did not coincide with the results of the liver biopsy study in 18.2% of cases. The histological diagnosis did not coincide with the clinical diagnosis in 5 (45.4%) patients and elastography in 3 (27.2%) patients. High rates from 3.22 to 12.05 were in 9 out of 11 (81.8%) examined patients in this group. In two patients (18.2%), the M2BP values were 0.35 and 1.55 and did not correspond to the severity of the process. With the developed LC, the

M2BP level was high except one patient with LC who had a low level of M2BP in the blood. Histological diagnoses were 100% consistent with M2BP in CHB. In CHB with Delta agent, M2BP values did not correspond to the histological diagnosis in only 13.3% of patients, which is significantly less than the errors of clinical diagnoses and indicators of liver elstography. With LC, low M2BP values were noted in only one patient. It is not advisable to use WFA+-M2BP with the generated LC HDV etiology as the clinical diagnosis in almost all cases corresponded to a histological diagnosis.

Thus, an important serum marker of chronic viral hepatitis B and D, reflecting the degree of hepatic fibrosis should be considered WFA+-M2BP. A prognostically favorable outcome of the disease should be associated with low value of WFA+-M2BP.

We calculated the correlation between WFA+-M2BP values and liver biopsy, and between WFA+-M2BP values and liver elastography.

Calculations were made using the formula.

$$r = \frac{\sum(X - x) \cdot (Y - y)}{\sum(X - x)^2 \sum(Y - y)^2)}$$

The following results were obtained. Correlation in both cases was positive. The correlation coefficient between WFA+-M2BP and liver biopsy results r=0.462068, that is, was >0<1. Figure 1 shows the correlation between these two indicators.

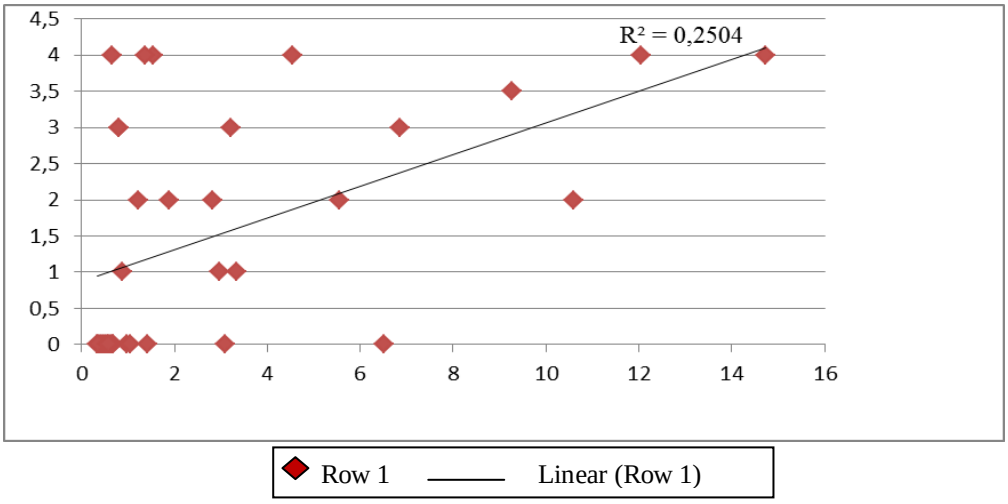

Fig 1: Correlation between WFA+-M2BP values and puncture liver biopsy (direct correlation).

A direct correlation was established between WFA+-M2BP values and the liver elastography. The correlation coefficient was r=0.524176. Figure 2. shows the correlation between WFA+-M2BP values and liver elastography.

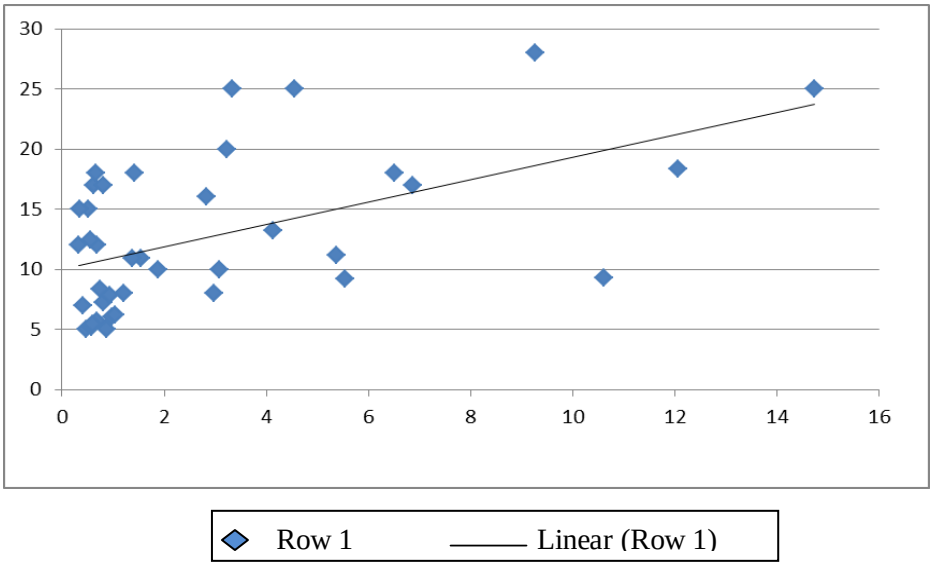

Fig 2: Correlation between WFA+-M2BP values and digital liver elastography.

In order to determine whether the calculations were reliable we used the Z test or the Fisher criteria according to the formula Z=1/2ln((1+r)/1-r)). The reliability of the results obtained by our calculations was: Z=0.499851. The confidence interval of the obtained data was calculated from the formula Z-1.96/√(n-3) to Z+1.96/√(n-3). The confidence interval was obtained from 0.173184 to 0.826518.

Thus, 95% of the data obtained from the calculation of the correlation between WFA+-M2BP and liver biopsy lie between 0.175 and 0.826, that is, above 0. According to the calculations, it can be seen that there is a correlation between the M2BP marker and the results of the biopsy, the correlation coefficient is 0.46, that is, greater than 0, and less than 1 (0 <r <1), indicating a positive linear correlation.

DISCUSSION

Direct and affordable methods for evaluating LF include ultrasonic liver elastography, which measures fibrosis based on transient elastography.[2,3,4] Evaluation of the severity of LF and the possibility of predicting the development of complications conducted by this method is considered to be convenient and accurate way that deserves wide application in practical public health.[5,6] Restriction of this method is ascites, excessive fatty tissue, biliary tract diseases, including cholelithiasis. Thus, some patients simply cannot conduct this study. Low sensitivity (66,0%) of elastography in the stages of LF F0-F1 dictates the need for using other tests to determine the degree of LF in these patients.[7]

Japanese researchers found that serum levels of glycosylated Wisteria floribunda agglutinin positive Mac-2 binding protein (WFA+-M2BP) may reflect the severity of LF in patients with CHB. We can summarize our studies on the evaluation of WFA+-M2BP as a diagnostic marker of LF and prognostic factor of the transition of CHB to LC.

If we summarize the available experimental data and a few hypothetical data concerning the role of the WFA+-M2BP serum marker in the evaluation of LF in chronic viral hepatitis and the study materials obtained by us, we can conclude that the serum WFA+-M2BP values may be useful for assessing the degree of LF in patients with chronic HBV and HDV infection. The results of the conducted studies indicate that the serum LF marker WFA+-M2BP is useful in chronic viral hepatitis for assessing the degree of liver damage.

Serum LF markers can be used in the clinical diagnosis of chronic hepatitis, but with histological signs of transition to LC. High indicators of WFA+-M2BP will help to correctly assess the patient's condition. With the development of LC, the use of serum WFA+-M2BP markers is not advisable, since the presence of clinical symptoms allows the diagnosis to be established accurately.

CONCLUSION

An important serum marker of chronic viral hepatitis B and D, reflecting the degree of fibrosis should be considered WFA+-M2BP. In CHB, histological diagnoses coincided with M2BP values. Prognostically favorable outcome of the disease in some patients should be associated with low values of WFA+-M2BP. Patients with a pattern of low or moderate chronic hepatitis, but with high WFA+-M2BP values, need close and longer follow-up, since normal ALT, absence of complaints and objective changes do not exclude the possibility of transition to LC. The levels of serum WFA+-M2BP can be used to interpret the prognosis of the disease.

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