Comparison of the diagnostic efficiency of various noninvasive methods for diagnosing liver fibrosis in patients with chronic viral hepatitis C

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Abstract

Summary: the article presents the results of the examination of patients with chronic viral hepatitis C namely the study of the informativeness of instrumental (fibroelastography) and serological (the content of hyaluronic acid in serum) of markers of fibrosis by assessing their predictive value by ROC- analysis.

The purpose of the study: to find out the possibility of non-invasive methods for diagnosing liver fibrosis in patients with chronic viral hepatitis C (CHC).

Materials and methods

66 patients with CHC with the 1-st genotype of the virus were examined, which were at the dispensary observation and ambulatory treatment at DCC CCH №1 in Vinnitsa and in the clinical department of viral hepatitis at the Institute of Epidemiology and Infectious Diseases named after L.V. Gromashevsky NAMS of Ukraine. All patients received fibroelastography (FEG) with a METAVIR score. All patients with CHC and group of control determined the content of hyaluronic acid (GA) in blood serum (ELISA using the Hyaluronic Acid (Corgenix, Inc., USA)).

Research results

Sensitivity of determination of GA in blood serum of patients with CHC with degree of fibrosis of liver F0-F2 was 91.23%, and specificity - 90.46%. For the FEG method, respectively: 74.33% and 77.25%.

In the group of patients with degree of fibrosis F3 sensitivity of the definition of GA in blood serum was 72.21%, and specificity - 74.71%. The corresponding qualitative characteristics for FEG were: 98.32% and 91.45% respectively.

The sensitivity of the determination of the content of GA in serum of patients with CHC with the degree of liver fibrosis F4 was 88.23%, and the specificity was 92.12%. For these patients the sensitivity and specificity of determining the degree of fibrosis by the FEG method were 87.78% and 91.45% respectively.

Conclusions

High diagnostic efficiency of determination of the content of GA in serum was established for assessing the degree of liver fibrosis in patients with CSF (AUC = 0,720-0,917, p<0,01). Relatively higher sensitivity and specificity of the diagnosis of liver fibrosis was observed in determining the content of GA in serum compared with the FEG method (AUC = 0.914 vs. AUC = 0.817 (p<0.05)) in the group with a lack or initial signs of liver fibrosis (F0-F2).

Key words: chronic viral hepatitis C, fibrosis, hyaluronic acid, fibroelastography.

Relevance of research

Chronic viral hepatitis C (CHC) is the current problem of the modern clinical medicine in Ukraine and in the whole world as well, in relation to the wide usage and to the fast development of liver fibrosis (LF) and as a result of the long conjunction of the immune cellular and the destructive process and, primarily, of the intense production of the stellar collagen cells and other components of the extracellular matrix with the further excessive accumulation that що leads to the destruction of the liver cytoarchitecture and the cirrhosis development [1, 2, 3].

With the appearance of the highly-efficient medication of the direct antiviral action revealing of the early fibrous changes in the liver prevents cirrhosis and hepatocellular carcinoma.

Popular noninvasive diagnostic methods LF include indirect fibroelastography (FEG) and serological markers. Ultrasound elastometry with the help of FibroScan belongs to the

direct methods of LF. This method allows to define the presence of LF by means of vibrational impulses, estimate elastic characteristics of the liver and tempo of LF development [4, 5]. Except that the influence of patient's overweight and hepatic steatosis on the FEG figures in some way restrict the usage of the above mentioned method [6].

This is the reason for continuation of searching for sensitive noninvasive diagnostic methods LF, results of which could tightly correlate with the data of liver-biopsy.

In the majority of the literature reviews prognostic role of the serological markers of liver fibrosis/ cirrhosis (stage F3-F4) is described, and also fibrosis in the intercurrent stages (F1-F2) [7, 8, 9]. The importance of establishment of the accepted liminal concentration of markers for defining of norms and pathologies, determination of the primary stages LF in CHC patients are relevant.

One of the predictors of LF is hyaluronic acid (GA), serous concentration of which is increased as a result of combining two processes: increase of collagen synthesis and та decrease of HA elimination from the circulation of endothelial cells of liver sinusoid [10, 11, 12].

In order to study informational content of the instrumental (FEG) and serological (GA content in blood cerum) fibrosis markers in the patients with CHC and estimation of their prognostic meaning (according to the logistic equation and discriminatory power) ROC-analysis was made.

The purpose of the study: to find out the possibility of non-invasive methods for diagnostics of liver fibrosis in patients with CHC.

Materials and methods

66 patients with CHC with the 1-st genotype of the virus were examined in order to solve the working tasks. Among patients there were 30 men (45,5%) and 36 women (54,5%), the average age was $34,5 \pm 1,12$ years. Patients were at the dispensary observation and ambulatory treatment at DCC CCH №1 in Vinnitsa and in the clinical department of viral hepatitis at the Institute of Epidemiology and Infectious Diseases named after L.V. Gromashevsky NAMS of Ukraine. According to the modern acts for diagnosis verification there were used definite criteria and patients' complaints, anamnesis data, and also information obtained from the clinical observation. Laboratorially CHC diagnosis was confirmed by means of defining in patients' blood cerum HCV-RNA with the help of the qualitative and quantative methods of polymerase chain reaction (PCR).

The activity of the necroinflammatory process was estimated and the stage of liver fibrosis was defined by means of (FibroScan, on the basis of the military-medical clinical

centre of the central region, Vinnytsia, the efferent therapy clinic, Kyiv) with the help of METAVIR. In 36,4 % (24 people) patients there was not any evidence of LF or any primary fibrosis F0 – F1, just the same amount of people had F2 fibrosis. Patients with fibrosis F3 were 18,2% (12 people). The characteristics of cirrhotic changes in the liver were defined in 9% of all observed people with CHC (6 people).

The control group included healthy people (n=21), representative with sex and age, with the fibrosis F0 according to METAVIR, with the normal results obtained from the liver function test or absence of liver diseases in anamnesis.

The estimation of HA content in blood serum was defined in all patients with HCH and people from the control group (in the scientific-research clinical diagnostic laboratory in VNMU named after M.I. Pirogov by means of immunoenzymometric method (ELISA) with the usage of set «Hyaluronic Acid» (Corgenix, Inc.,США)).

Statistical processing of results was held in the system of statistical data analysis Statistica 10.0.288.8 Portable.

In order to get the certain data according to the logistic equation and definite defining of discriminative ability of different results the ROC-analysis was held, that includes formation and analysis of curved operational characteristics, determination of square under ROC-curve (AUC — area under the curve) with the standard square defect under the curve and 95 % interval; indices of sensitivity (Se) and specificity (Sp). ROC- analysis was considered adequate because of difference between AUC and value 0,5.

Research results and discussion

According to the results sensitivity of determination of GA in blood serum of patients with CHC with degree of LF F0-F2 was 91.23%, and specificity - 90.46%. (picture 1). For the FEG method, respectively: 74.33% and 77.25%. Square under the curve (AUC) was 0,914 (p<0,001), that corresponds to the high importance of the following method of defining LF.
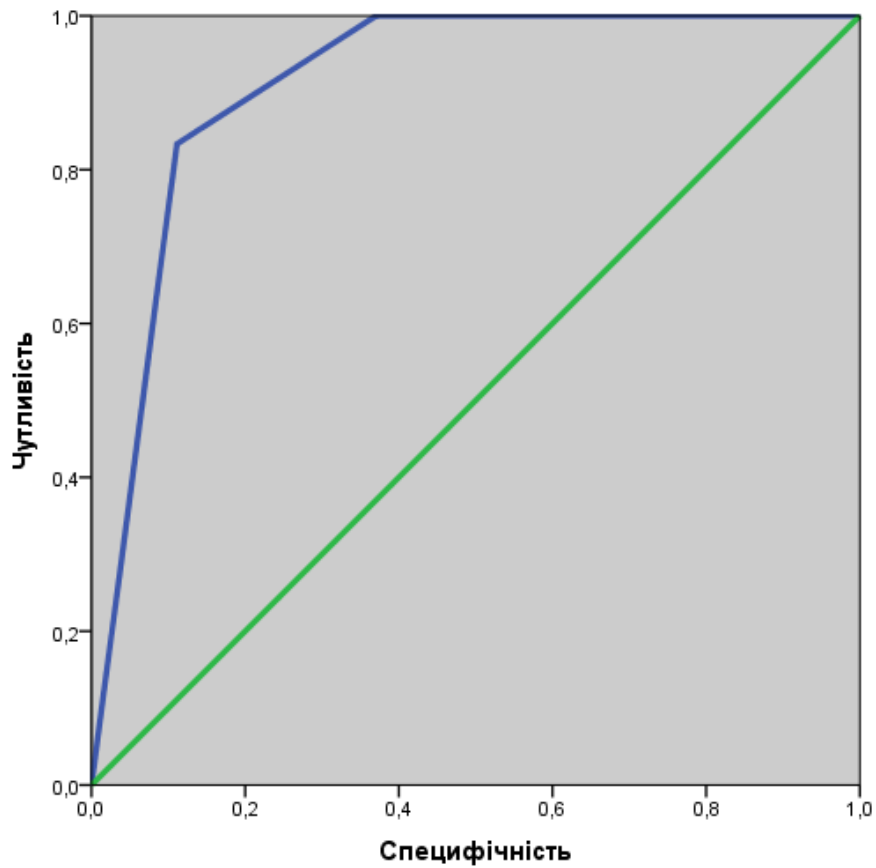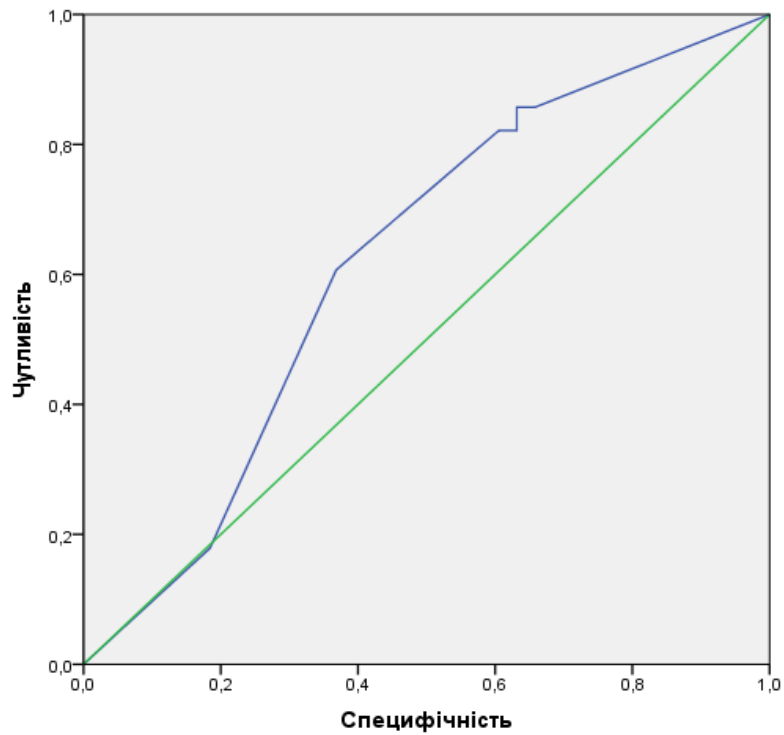
Picture 1. ROC – curve: determination of the content GA in the blood serum in the patients with LF F0-F2.

At the same time the sensitivity of the determination of the stage of LF with the help of FEG in the patients with HCH (F0-F2) was only 74,33%, and specificity - 77,25% (AUC=0,817 (p=0,011)) (picture 2). The sensitivity of the determination of the content of GA in serum of patients with CHC with the degree of LF was higher in 1,12 times than the value of determination of LF by means of FEG in the patients with CHC with the degree of LF F0-F2.
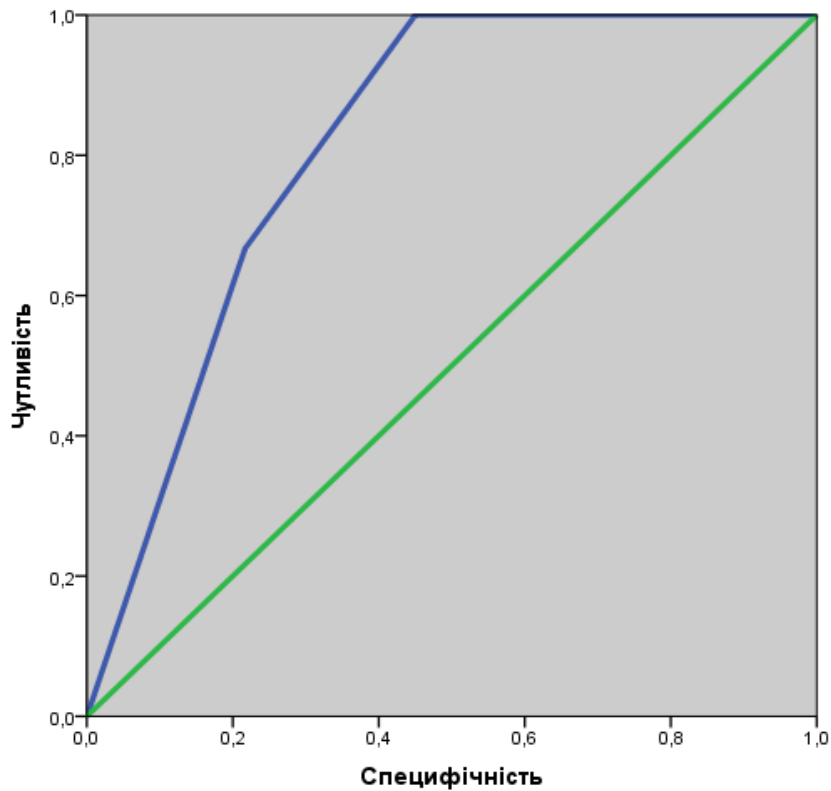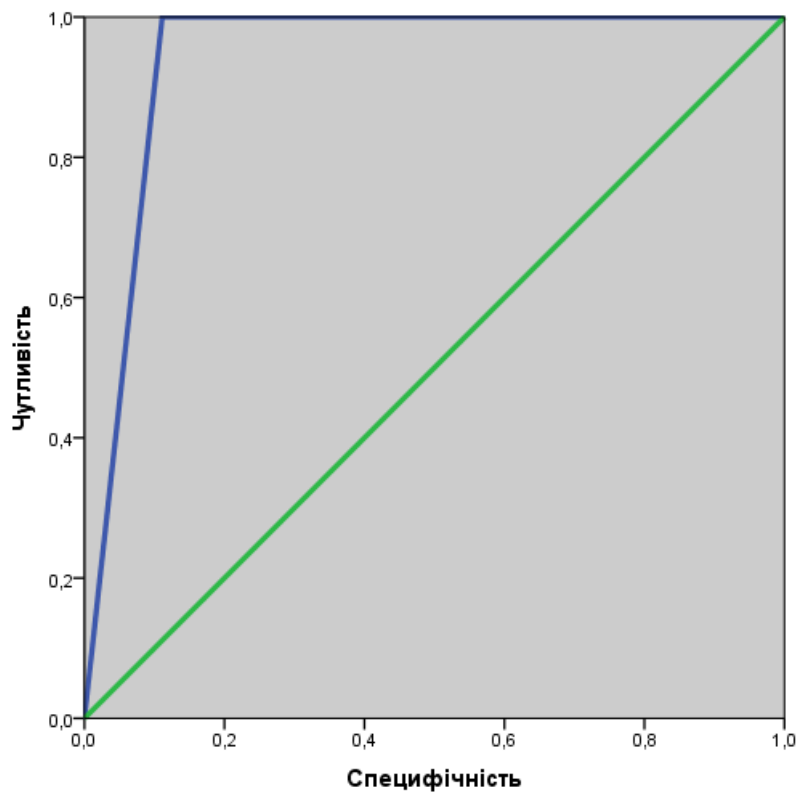
Picture 2. ROC – curve: determination of the degree of liver fibrosis with CHC in the patients with LF F0-F2.

Another situation was in the group of patients with CHC with the defined LF (F3), in which the value of GA in the blood serum had the average figure (AUC=0,720 (p=0,0098)). In the group of these patients sensitivity of the definition of GA in blood serum was 72.21%, and specificity - 74.71% (picture 3). In the group of patients with HCH with defined degree of liver fibrosis (F3) the corresponding qualitative characteristics for FEG were: AUC=0,944 (p=0,001) and were higher in 1,31 times in comparison with definition GA in the blood serum. The sensitivity of this method was 98,32 %, and the specificity -91,45% (picture 4).
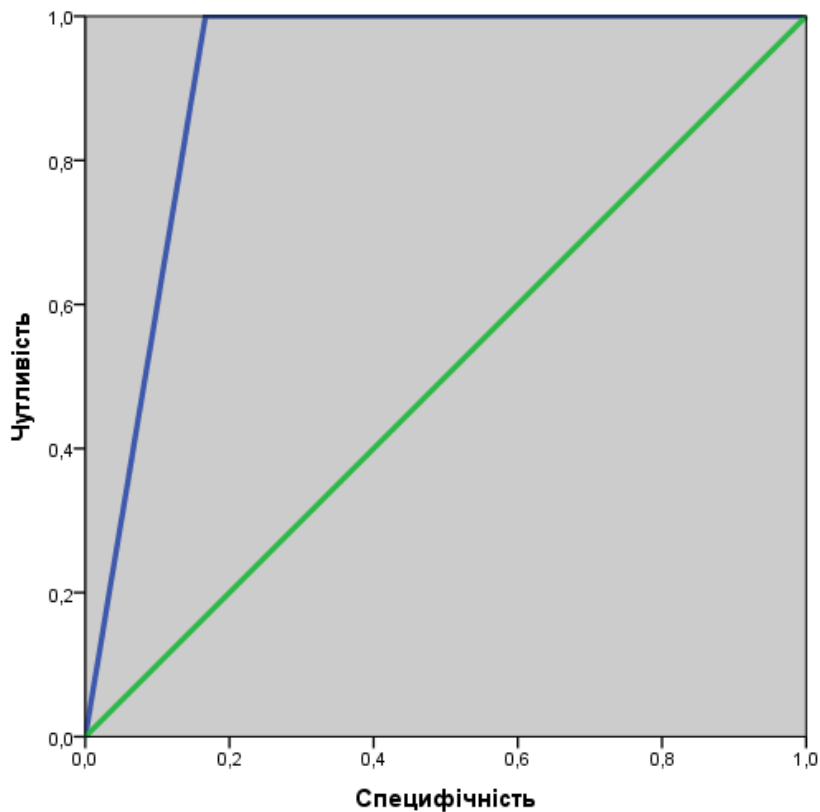
Picture 3. ROC – curve: determination of the content GA in the blood serum with CHC in the patients with LF F3.
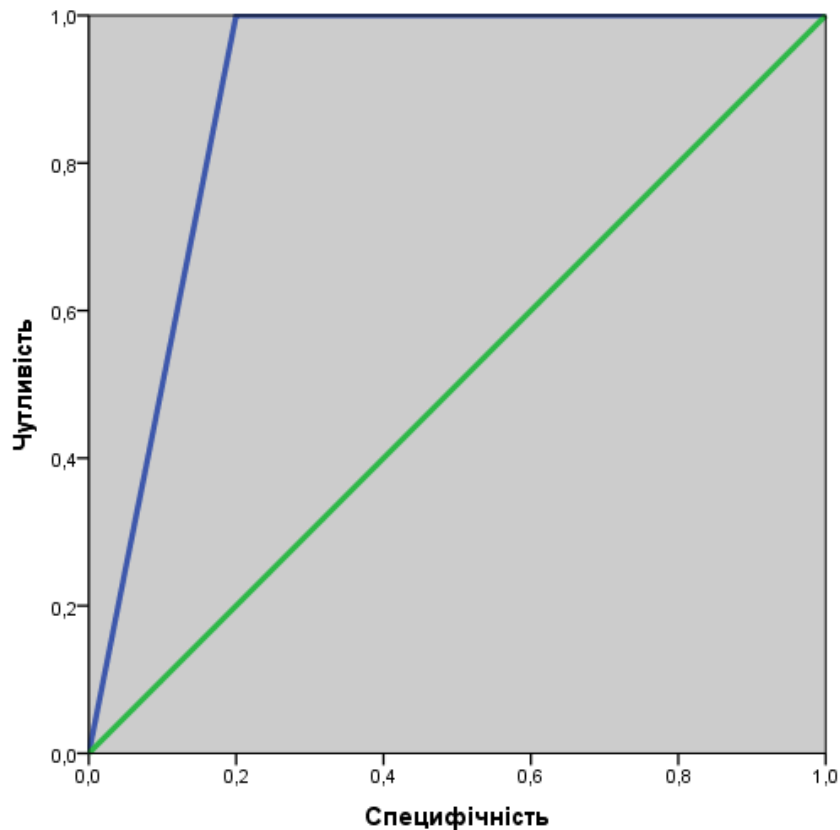

Picture 4. ROC – curve: determination of the degree of LF with CHC by means of FEG with LF F3.

For patients with HCH with the cirrhotic changes in the liver (F4) we defined the high sensitivity and specificity of both diagnostic techniques that were compared. The sensitivity of the determination of the content of GA in serum of patients with CHC with the degree of liver fibrosis F4 was 88.23%, and the specificity was 92.12%, AUC=0,917 (p=0,001) (picture 5).

Picture 5. ROC – curve: determination of the content GA in the blood serum in the patients with CHC with LF F4.

For these patients (the degree of LF was F4) the sensitivity and specificity of determining the degree of fibrosis by the FEG method were 87.78% and 91.45% respectively (AUC=0,900 (p=0,01)) (picture 6). We did not determine the definite difference between the sensitivity and specificity of both diagnostic methods of liver fibrosis in the patients with CHC and with characteristics of LF F4.

Picture 6. ROC – curve: determination of the degree of LF with CHC by means of FEG with LF F4.

Conclusions

High diagnostic efficiency of determination of the content of GA in blood serum was established for assessing the degree of LF in patients with CHC (AUC = 0,720-0,917, p<0,01).

In the group of patients with CHC with absence or primary characteristics of LF (F0-F2) relatively higher sensitivity and specificity of liver fibrosis diagnostics was observed while defining the content of GA in blood serum compared with the FEG method (AUC = 0.914 vs. AUC = 0.817 (p<0.05)).

In the patients with CHC with the evident liver fibrosis diagnostic efficiency of the FEG method was statistically higher (AUC=0,944), but for the method of GA determination in blood serum the corresponding index was 0,720 (p<0,01).

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