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LIVER AND SPLEEN ELASTOGRAPHY IN PATIENTS WITH DIFFUSE LIVER DISEASES

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Abstract

The purpose of the research was to estimate the clinical-diagnostic and predictive value of non-invasive ultrasonic elastography in dynamic monitoring in patients with diffuse liver disease. 114 patients with diffuse liver disease were examined, specifically 68 (59.6%) men and 46 (40.4%) women. The patients were divided into three groups: 40 patients with steatosis; 38 – with hepatitis; 36 – with cirrhosis. The research included clinical and bio-chemical analysis, ultrasound examination of liver and spleen with doppler v. portae and v. lienalis, elastography of liver and spleen. The study found a high correlation of elastography data as regards the liver and spleen in patients with alcoholic cirrhosis ($r = 0.96$), average correlation ($r = 0.69$) in patients with steatosis and hepatitis of alcoholic etiology. On the basis of the statistical program ROC-analysis it was ascertained that the spleen is in perfect condition (AUC 0.9-1.0), and the liver is in a very good condition (0.8-0.9). The research revealed therapeutically significant factor $\Delta F / \Delta L$ for dynamic monitoring: the $\Delta F / \Delta L \geq 1$ can predict a more favorable course of the disease. Non-invasive ultrasound elastography helps to forecast the process of the disease and correct the therapeutic approach. The research contributes to the search for additional and reliable techniques of identifying the stage of disease of patients with hepatic fibrosis, the dynamics of the disease as well as forecasting further complications.

Introduction

Diffuse liver diseases (DLD) dominate the prevalence and mortality causes, especially among etiological groups of liver diseases. DLD combine various disorders of the structure and functional ability of the organ, caused by prolonged and systematic use of alcoholic beverages^{1,2}. Alcoholic liver diseases are the prevailing ones in terms of incidence and mortality in all etiological groups of liver diseases. Alcoholic liver disease encompasses various types

of structural damage and disruption of the functional capacity of the organ caused by long-term and regular consumption of alcohol. Alcoholic liver disease occupies the second place in the prevalence and social significance after acute and chronic viral liver disease. Currently, the main problem of hepatology is cirrhosis, usually associated with chronic alcohol intoxication, etc.³. Increased consumption of alcohol by the country's population has led to a growing number of patients with alcoholic cirrhosis. Alcoholic cirrhosis has killed 3.5 times more patients than viral hepatitis. In most cases, these people were of working age⁴⁻⁶.

The prognostication of DLD and choice of treatment for patients depend on the severity of the fibrous process in the liver, which has an impact on the terms of progression of the underlying disease, serves as a criterion of drug therapy effectiveness, and determines the risk of adverse outcomes⁷. Liver biopsy is an invasive and painful technique, associated with a risk of complications after treatment, while the analyzed fragment of the liver tissue may not reflect the changes that occur in the organ overall⁸. The histological assessment of liver fibrosis may be inaccurate and often depends on the experience the histologist. Serological markers – AST / ALT, platelet count, prothrombin index, and the AST / platelet count correlation – may indicate the presence of pronounced liver fibrosis, but their value can vary with other diseases or under the effect of a different therapy^{9,10}. Therefore, it is necessary to find an additional technique to determine reliably, without compromising the health of patients with DLD, the stage of the disease, to assess the severity of fibrosis, including changes over time, and to prognosticate further pathology and complications^{11,12}.

Thus, the task of noninvasive diagnostic techniques in cases of liver fibrosis and its complications in patients with DLD by noninvasive liver and spleen ultrasonic elastography is a relevant problem of modern Russian and world health¹³⁻¹⁵.

The purpose of the present study is to assess the clinical diagnostic and prognostic value of noninvasive ultrasound elastography in dynamic monitoring of patients with alcoholic liver disease¹⁶⁻¹⁸.

Materials and Methods

From 2008 to 2015, 114 surveyed patients with DLD (68 (59.6%) men and 46 (40.4%) women) were hospitalized at the gastroenterology department of Clinical City Hospital No. 1 (Smolensk), where they received treatment. All patients were divided into 3 groups: 1st group – 40 patients with steatosis (main group); 2nd group – 38 patients with hepatitis; 3rd group – 36 patients with liver cirrhosis in compensation and decompensation¹⁹.

The criteria for inclusion in and exclusion from the study were as follows:

Inclusion criteria

- Men and women with DLD over the age of 18;
- Patients with diagnosed DLD;
- Patients with diagnosed morphologically verified DLD.

Exclusion criteria

- Signs of portal vein thrombosis after Doppler ultrasound examination;
- History of arterial / venous thrombosis, including Budd-Chiari syndrome;
- Any pathological condition, associated with currently active bleeding;
- Pregnant or lactating women ^{20,21}.

The nature of DLD was determined by the clinical and biochemical parameters of the blood. The laboratory analysis determined the basic parameters of the general (erythrocytes, hemoglobin, white blood cells, erythrocyte sedimentation rate) and biochemical (total protein, total bilirubin, ALT, AST, GGT, alkaline phosphatase) analysis of blood ²². The indicators reduced after 6 and 12 months of observation in the course of the treatment. The comprehensive diagnostic algorithm included consultations of a psychiatrist and neurologist. The list of mandatory research and treatment techniques was in full compliance with the standard of the Ministry of Health and Social Development of the Russian Federation No. 404 dated 26.05.2006 and the decree of the Ministry of Health and Social Development of the Russian Federation No. 415n dated 02.06.2010.

All main group patients (n = 114) were managed at the hospital in accordance with the decree of the Ministry of Health and Social Development of the Russian Federation No. 1 dated 17.01.2007 in the following order: admission – examination, laboratory tests, liver and spleen ultrasound with duplex scanning of v. portae u and v. lienalis, liver and spleen elastography.

Liver biopsy served as the reference method when diagnosing liver fibrosis (n = 47) ^{23,24}. A clinical examination was conducted over time, including a survey of patients, physical examination, laboratory tests, liver and spleen ultrasound with duplex scanning of v. portae u and v. lienalis, and liver and spleen elastography (in 15 days, and then after one, three, six, nine, and twelve months).

During the laboratory analysis, patients' basic biochemical parameters (total protein, total bilirubin, ALT, AST, GGT, ALP) were as follows.

Two main ultrasound techniques were used: B-mode and duplex scanning. B-mode scanning was performed by ultrasonic scanners Aloka SSD-4000, Hitachi EUB-525, and Sonoscape S-8. Linear and Convex 3.5 and 5.0 MHz electronic sensors were used. Ultrasound assessed the following parameters: diameter of the portal and splenic veins (in mm), maximum linear velocity of blood flow in the portal and splenic veins (V_{max} , cm / s), mean linear velocity of blood flow in the portal and splenic (V_{mean} , cm / c), and the volume flow rate in the portal and splenic veins (FW, l / min) ²⁵⁻²⁷. In addition, it evaluated the dimensions (in mm) of the right lobe of the liver (length, width), the left lobe of the liver (length, width), and the diameter of spleen. The analysis of the blood flow depended on the F-change in the liver and the L-change in the spleen, which is a diagnostic value in determining the extent of perfusion disorders with DLD.

For more accurate an aspect of the intensity of changes not only in liver, but also in the spleen of patients with DLD, the present study offered an improved technique of a comprehensive multifocal elastographic examination. This technique involves measuring the elasticity of the liver and spleen, the coverage of a large volume of tissue in patients with DLD, and specifying data of liver and splenic parenchyma echosemiotics by preliminary ultrasound ^{28,29}.

Essentially, the technique is a multifocal and comprehensive examination.

Transient elastography (Fibroscan) is a promising technique for evaluating the degree of elasticity of the underlying organic tissue. A sensor mounted on the abdomen transmits low-frequency vibrations. Vibrations induce a low-frequency shear wave that propagates faster in denser tissue. The indication for ultrasound elastography is the presence of diffuse liver diseases of various etiologies. Elastography is performed with the Fibroscan device (Echosens, France) ³⁰⁻³³.

A retrospective (n = 33) and prospective (n = 10) analysis of the pathological findings for patients with various forms of DLD during three years with an impact analysis of statistical correlations of the histological structure of the liver and spleen, and elastographic indices of said organs were carried out to confirm elastographic changes in the liver and spleen ^{34,35}.

Research results were processed statistically in the original database in Microsoft Excel 2007 with the Statistica 7.0 software package. During the analysis of the material, the mean value (M), standard errors (m), standard deviation (SD), and 95% confidence interval were calculated.

Since most samples are subject to the normal distribution law, data are presented as $M \pm m$ for the purpose of

unification. Mathematical processing of the results was performed by variation statistics techniques – Student’s t test and Mann-Whitney nonparametric test (to compare two independent unrelated groups), depending on whether the value of the normal distribution law was investigated.

In addition, the statistical test used the Fisher multi-angular transformation to compare fractions. Differences were considered significant at a probability level of $p < 0.05$, permissible in medical researchers.

The sensitivity level of diagnostic techniques of liver and spleen elastography were determined by ROC analysis (Receiver Operator Characteristic) with the SPSS 20.0.5 statistical package³⁶.

Results

When analyzing the diameter of the portal and splenic veins in the studied groups and comparing it to the control group, a statistically significant increase was found in the diameter of these veins in all treatment groups, compared with the control group ($p < 0.001$); based on obtained data, it should be noted that the decrease of blood flow velocity indices in the portal veins and the spleen was significantly greater with alcoholic cirrhosis, accompanied with an increase in the vein diameter (Figure 1, Figure 2).

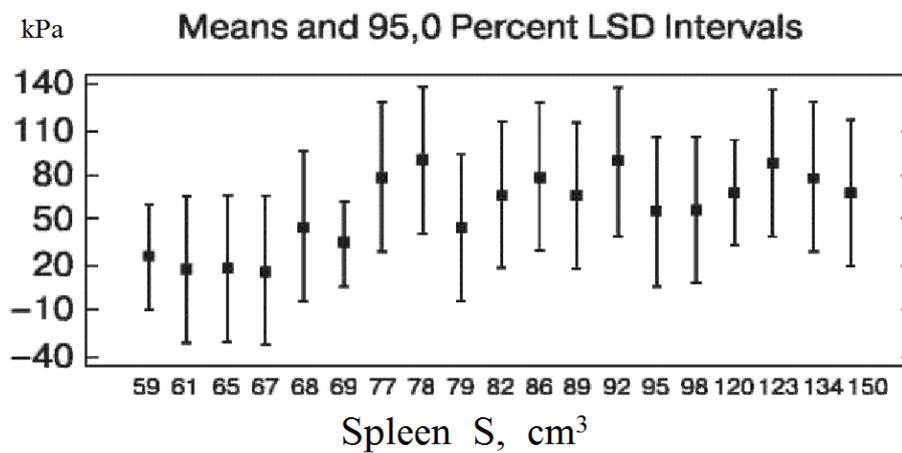


Figure-1

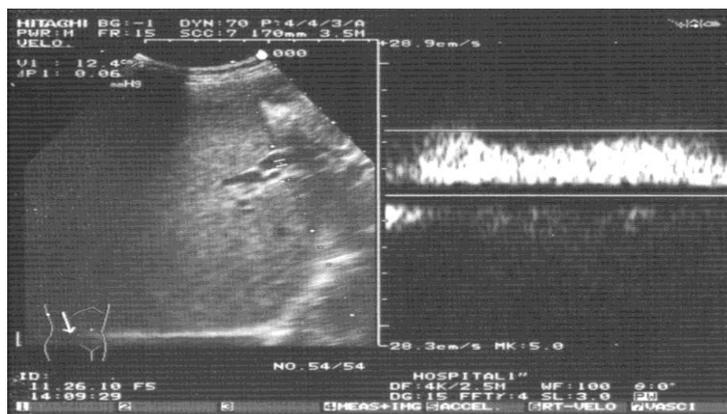


Figure 2. – Ultrasound tomogram of dopplerometry in CFM mode of the v. portae in an ALD patient.

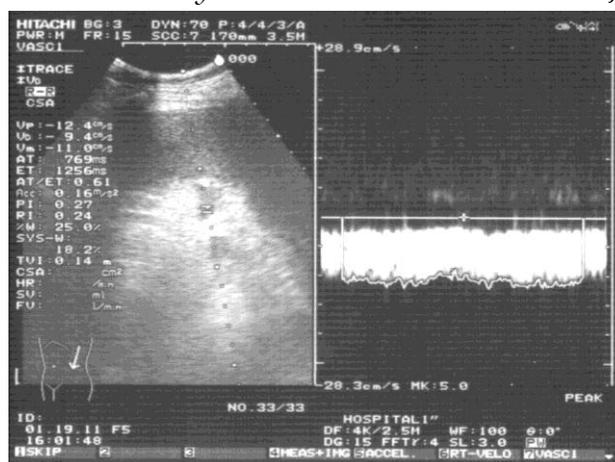


Figure 3. – Ultrasound tomogram of dopplerometry in CFM mode of the v. lienalis in an ALD patient.

This is indicative of a growing vascular resistance with a restructuring of the hemodynamics hyper-dynamic type.

The slowing the blood flow rate in the portal vein was in proportion to the degree of fibrosis of the liver parenchyma and fibrosis of the pulp of the spleen ($p < 0.001$).

With respect to the splenic vein, it should be mentioned that it is expanding due to the stagnation of blood flowing through it into the portal system. A splenic vein diameter of 8 mm is an indirect sign of portal hypertension. The degree of expansion depends on the severity of the underlying disease process, the degree and location of operation collaterals. Blood flow in the vein slows down and can even reverse.

Due to prolonged stagnation of blood in the splenic vein and gate, varicose deforms its walls, which become thinner. Therefore, based on data, obtained from the histopathological examination, the slowing of the blood flow in the splenic vein is an indirect sign of microcirculation and the development of sclerosis of the pulp and / or capsules.

When comparing the Vmax of the portal vein in the main and control groups, its reduction was found only in the 2nd and 3rd groups. When comparing the Vmax in the studied groups, the 3rd and 2nd group showed a significant decrease in this indicator, compared to the 1st and control groups.

During the analysis of the splenic vein Vmax, there was a statistically significant decrease in this indicator in all three patient groups, compared to the control group. The volumetric flow rate (FR) was significantly lower in three groups, compared with the control group.

The analysis of ultrasonic parameters of the liver and the spleen, depending on the F-L-changes.

With an increasing degree of liver fibrosis, its size has also increased in ultrasound. It is also worth noting the greater growth of the left lobe of the liver – by 1.8 times from $x 57.4 \pm 5.5$ 45.6 ± 4.3 109.7 ± 7.3 to 85.4 ± 4.5 x mm ($p < 0.05$), the growth of the right lobe was less significant – by 1.3 times: from $128.0 \pm 5.2 \pm 3.3$ x 100 to 168 x $128 \pm$

5.4 ± 6.2 mm (p<0.05). Fibrosis is more related to the size of the left lobe: r = 0.50 (p<0.05), than the right lobe: r = 0.44 (p<0.05). A less pronounced positive correlation was observed between the size of the spleen and the degree of fibrosis: r = 0.29 (p>0.05) with spleen length, r = 0.12 (p>0.05) with spleen diameter. Increase in the size of the spleen indicated developing portal hypertension, caused by an increase in the intrahepatic vascular resistance due to compression of enlarged hepatocyte sinusoids. This was evidenced by the changing parameters of arterial and venous perfusion of the liver.

In order to evaluate the treatment of alcoholic liver disease it was necessary to conduct dynamic elastography monitoring, which helped forecast the progression, and stabilize and/or regress fibrosis. The case follow-up of patients during the year found a change in elastographic indicators (in kPa) of the liver in all clinical forms of alcoholic liver disease. The evaluation of the elastography stages of patients with steatosis showed a shift from the F2-F1 stages to F0; with hepatitis – from F3 to F2 – the with a move favorable prognosis; with hepatic cirrhosis, despite variations in elastographic indicators, patients remained at the F4 stage, which indicated the need to monitor how patients observed treatment more frequently (Fig. 1).

The assessment of elastographic indicators with splenic steatosis throughout the observation period showed the persistence of the L1 stage; in cases of hepatitis and cirrhosis of the liver – the L4 stage; elastographic indicators in cases of liver cirrhosis were three times higher than in cases of hepatitis (p<0.05). After 12 months of treatment, patients with hepatitis shifted from the L4 stage to the L2 stage; patients with cirrhosis remained at the L4 stage, but elastographic indicators decreased by three times (p<0.05), indicating a favorable course of the disease (Fig. 2).

The authors investigated the correspondence between L-changes and the size of the spleen (Fig. 3). The size of the spleen ranged from 59 to 150 cm³; in addition, it was found that kPa obtained with transient spleen elastography did not depend on the abovementioned results, i.e. the elastographic indicators could be high with normal or enlarged spleen size. Thus, a high correlation was established between the area of L-changes and spleen ultrasound results, in particular, the larger the size, the greater the value of L-kPa in the L-stage (r = 0.828, p = 0.046). There is an additional correlation with the progression of DLD, when the area and the ultrasound size of the spleen may be normal with increased kPa values (r = 0.923, p = 0.057).

Obtained results of the dynamic study of the liver and spleen were compared with the results of the histological organ material, which enabled compiling a modified METAVIR score for the spleen (Table 6).

The $\Delta F / \Delta L$ ratio was introduced to evaluate the prognosis of the clinical course of DLD. The ratio reflects particular indicators for each patient, expressed in units, namely >1 or <1 . The analysis of changes over time in elastographic indicators in the first subgroup showed that the $\Delta F / \Delta L$ ratio during the entire follow-up period was >1 .

The analysis of the ratio in the second subgroup on admission and before the ninth observation month showed that $\Delta F / \Delta L < 1$, while on the twelfth observation month, $\Delta F / \Delta L > 1$. The analysis of the ratio in the third group on admission and before the sixth observation month showed that $\Delta F / \Delta L < 1$, while on the ninth and twelfth month, $\Delta F / \Delta L > 1$.

Thus, the favorable course of DLD can be judged by the $\Delta F / \Delta L$ ratio if it >1 , while $\Delta F / \Delta L < 1$ indicates a possible adverse outcome. The presents the characteristics of the liver and spleen elastography of all 114 patients.

Follow-up spleen elastography found that in 26 (68.4%) patients with F1-F2-F3 fibrosis, according liver and spleen elastography the index was L4. Upon further observation of these patients after three-six months, they were diagnosed with cirrhosis of the liver; these patients died; the $\Delta F / \Delta L$ ratio was <1 .

Thus, if the $\Delta F / \Delta L$ ratio >1 during case follow-up, it is possible to predict a more benign and stable disease course, F-numbers, and L-change. If the $\Delta F / \Delta L$ ratio <1 during case follow-up, it can be regarded as a predictor of a pre-cirrhosis state and possible death. Hypothesis testing for compliance of data with developed diagnostic criteria was carried out by determining the sensitivity and specificity of the built ROC curve and calculating the area under the curve – AUROC, which characterized the test indicator for sensitivity and specificity, its diagnostic and prognostic value (Fig. 4).

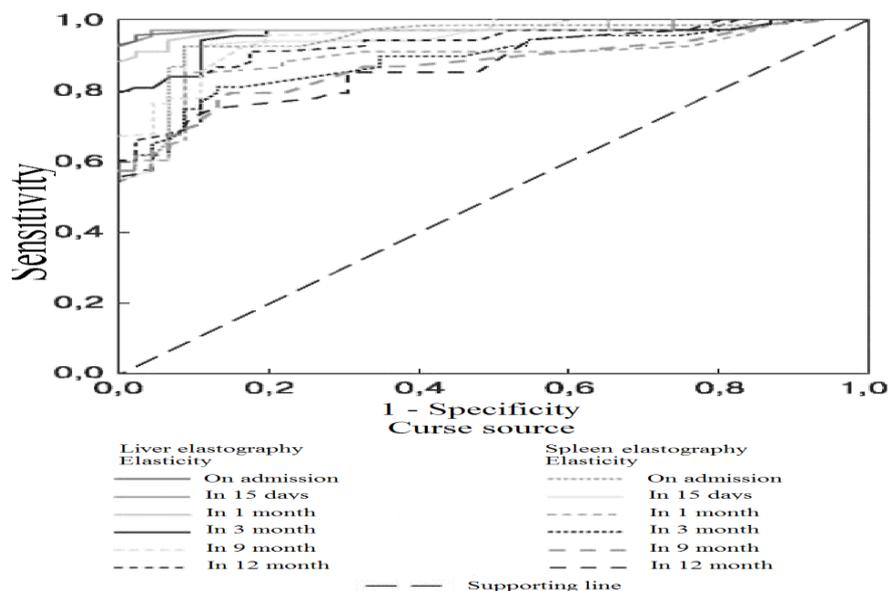


Figure-4

Discussion

To date, there is not enough information on the application ultrasound elastography on patients with DLD. Despite a sufficient number of scientific publications about elastography, authors do not indicate the possibility of using spleen elastography to assess the prognostication of DLD complications. A multifocal examination of the liver and spleen is not considered in any publications. In terms of hepatic parenchyma, it is known that the progression of the fibrotic process is uneven. Authors do not indicate the earliest possible changes in the spleen; no sources mark anatomic pathological changes, occurring in the spleen during the progression of DLD. The study of these issues is of particular interest.

The authors generalized obtained statistically significant data, which allows concluding that noninvasive multifocal liver and spleen ultrasound elastography is effective for the early diagnosis of DLD. To assess the clinical prognosis in all studied groups, ultrasound elastography was performed several times (on admission, in 15 days, and then after one month, three months, six months, nine months, and twelve months). These data show a significant difference in elastography indicators of the liver and spleen (in kPa) throughout the entire observation period in all three studied groups and the control group ($p < 0.05$). Moreover, in full concordance with the medical recommendations for alcoholic steatosis and hepatitis patients, a decrease in elastographic indicators was observed during the observation from three to twelve months, which was not observed in cases of cirrhosis of the liver, which confirms the irreversibility of the cirrhotic process. After obtaining the abovementioned results, the authors set goal of studying the pathological material of deceased patients by preliminary elastographic intravital examination of the liver and the spleen. It was necessary to modify the METAVIR score for the previous elastographic spleen examination.

Conclusion: 1. The algorithm of the use of noninvasive ultrasound elastography for improving the technique, particularly, based on a multifocal comprehensive examination of the liver and the spleen, helps doctors to predict the further course of the disease and timely adjust the patient's treatment.

2. There is a high correlation in the data of liver and spleen elastography in patients with alcoholic cirrhosis ($r=0.96$), average correlation ($r=0.69$) in patients with steatosis and alcoholic hepatitis.

3. Based on the results of the clinical, instrumental, and morphological comparison, a high risk of developing cirrhosis of the liver is confirmed before the appearance of clinical signs by additional liver and spleen elastography, which is proven by ROC analysis: perfect quality model of the spleen (AUC 0.9-1.0) and very good quality model of the liver (0.8-0.9).

4. The discovered therapeutic significance of the $\Delta F / \Delta L$ ratio in case follow-up is as follows: $\Delta F / \Delta L > 1$ can predict a more favorable course of the disease; if the $\Delta F / \Delta L$ ratio during case follow-up < 1 , it can be considered a predictor of cirrhosis and a possible adverse clinical outcome.

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Borsukov Alexey, Morozova Tatiana, Kovalev Alexey declares that they have no conflict of interest and sources of funding. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants.

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