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INTERDISCIPLINARY TOPICS

LIVER ELASTICITY AS A MEASURE OF LIVER DAMAGE

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Abstract: The prospective study was conducted over a 24 month period among newly diagnosed patients with viral hepatitis B and C. The aim of the study was to investigate the influence of age and liver elasticity on the chance of hepatocellular carcinoma development. The results showed that both hepatitis and age over 50 yrs lead to high level of liver stiffness. The patients over 50 yrs have 3.25 times higher odds of increased LS compared to those under 50 in case of HCV and 2.15 times higher odds in case of HBV. It was established that the patients in risk (those which liver stiffness is over 13 kPa) are between 18% for HBV and 25% for HCV. The results are statistically significant when LS is greater than 15 kPa.

Key words: elastography, liver stiffness, viral hepatitis B and C.

1 Introduction

Elastic modulus is a measure for diagnostic of mechanical properties of different materials–solid materials, hydrogels, biomaterials, organs and tissues [1–3]. The slope of the stress-strain curve in the elastic region obtained after testing of a material is defined as the Young's modulus (E) - a measure of a material's stiffness. In some cases a secant modulus is calculated, defined as a ratio of the stress and preset value of a strain [4]. For elastic and orthotropic materials is possible to determine the orthotropy ratio calculated as the ratio of Young's moduli of samples investigated in orthogonal directions [5].

Traditionally liver structure is assessed through palpation, blood tests and biopsy. The biopsy is considered the most realistic method for evaluation of liver structure. The biopsy depends on the location of the sample and allows an analysis of a very small portion of the liver. Although a complication rate of the biopsy is low (approximately 3%), this is an invasive method and is not suitable for repeated applications

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and disease monitoring [6]. All these reasons lead to its decreasing acceptance by patients [7].

Today the preferred methods for the assessment of liver changes are noninvasive methods such as serum markers, echocardiography and elastography (ultrasound (US) and magnetic resonance (MR) imaging) [8, 9]. Echography is an imaging study that presents changes in the structure and dimensions of the organ, while elastography helps to determine the physical properties of the tissue [8].

The main idea used in constructing the devices for noninvasive investigation of tissues and organs is to apply a mechanical stimulus – pressure or a transverse wave and to measure the deformation of the tissue or the velocity of the transverse wave. According to the applied external load, the measured physical quantity and the method for presenting the results, elastography is divided into: strain elastography (elastography, measuring the deformation), transient elastography, (the speed of wave created through low-frequency vibrations is measured) and imaging diagnostics [8–10]. Transient elastography (TE) and acoustic radiation force impulse (ARFI) techniques (point shear-wave elastography (pSWE) and two-dimensional (2D) shear-wave elastography (SWE)) are a part of US elastography methods [8, 9].

The FibroScan system (Echosens, Paris, France) was the first commercially available TE system, introduced in Europe in 2003 and approved in the United States in 2013. The FibroScan probe delivers a 50-Hz mechanical impulse to the skin surface and then measures the velocity of the generated shear wave. FibroScan uses M probe for standard examinations (depth 25–65 mm and lower operating frequency 3.5 MHz) and the XL probe for overweight patients (depth 35–75 mm and frequency 2.5 MHz) [8]. ARFI elastography techniques use focused US pulses to deform internal tissue and generate shear waves [11]. ARFI methods operate at frequencies of 100–500 Hz [12]. Clinical US elastography systems report "stiffness" in terms of the Young modulus or shear-wave speed. MR elastography reports the shear stiffness of tissue, which is the magnitude of the complex shear modulus $|G^*|$. Shear-wave speed and Young modulus E are related by the following equation: $E = 3\rho c^2$, where c is the shear-wave speed and ρ is the density of the tissue [8].

The most widely used method for evaluation of liver stiffness in clinical practice is transient elastography (TE, Fibroscan). It provides more realistic results for the state of the liver because measures liver elasticity in a volume at least 100 times larger than that of a liver biopsy [13]. The result presented in terms of Young's modulus vary between 2.5 and 75 kPa [14–16]. Chronic liver diseases can lead to liver fibrosis, which end-stage is cirrhosis and in some cases hepatocellular carcinoma (HCC) [8]. The phases of cirrhosis are compensated (stage 1 and stage 2) and decompensated (stage 3-–stage 5). Stages 1 and 2 have low mortality rate 1.5–2%. Progression rate from stage 1 to stage 2 is about 6.2% or to stage 3 or 4 about 4.2%. Transition from stage 2 to decompensation (stage 3 or 4) happens in 12.2% patients per year. Stage 3 is characterized by bleeding of the gastrointestinal tract and portal hypertension. One year mortality rate is 10% and 21% of patients develop mostly ascites per year. During Stage 4 the patients suffered from ascites, jaundice or encephalopathy. One year mortality rate increases to 21%; rate of transition to last stage is 10% per year. The patients in last stage have more than one complication – ascites, encephalopathy, acute kidney injury and advanced liver dysfunction. One year mortality in this stage is at least 27% and the severity of decompensation is up to 57% [17].

The increased rigidity of the liver is associated with increase in the stage of fibrosis and this fact is used in elastographic methods. According to Sporea and Sirli when the Young modulus is in the interval [2.5–7 kPa] there is absence of fibrosis or it is minimal [16]. Young modulus between [7–9.5 kPa] is a sign of a moderate fibrosis. When E is in the interval [9.5–13 to15 kPa] it is sure that severe fibrosis exists and over 15 kPa the patient suffers from liver cirrhosis [16].

The liver stiffness(LS) of Bulgarian patients is investigated from clinical point of view in the studies [18–23]. Antonov et al. used Fibroscan for evaluation of liver fibrosis among patients with chronic HBV and HCV infections. The authors compared liver stiffness measurement to METAVIR score obtained after histology and concluded that there was statistically significant correlation between LS and METAVIR stage of fibrosis in both type of hepatitis. LS cut-off values and ranges are supported by a level of sensitivity and specificity [18]. R. Balabanska applied transient elastography in the assessment of hepatic steatosis and non-alcoholic steatohepatitis, while R. Tsonev evaluated liver fibrosis and quality of life in patients with chronic viral hepatitis C and cirrhosis [19, 20].

Ivanova et al. investigated the role of liver stiffness measurement by transient elastography in patients with chronic liver disease [21]. LS was found to be strongly associated with transaminase activity, prothrombin time and platelet count. The cirrhotic patients LS was 18.72 kPa. The diagnostic accuracy of elastography for cirrhosis at threshold of 14.5 kPa was 88.9% [10].

B. Hristov et al. used two-dimensional shear wave elastography (2D-SWE) as a predictor for the presence and severity of esophageal varices (EVs) in cirrhotic patients with clinically significant portal hypertension [22]. Doykova et al. presents a comprehensive research on the stiffness of the liver and spleen performed by pSWE in patients with chronic viral hepatitis, as well as evaluation of their correlation with the histological assessment of liver fibrosis [23].

The results about liver elasticity can be used in clinical practice for predicting complications in case of viral hepatitis B and C. The aim of the study is to investigate the influence of age and liver elasticity on the chance of hepatocellular carcinoma development and to assess the expectable cases of hepatocellular carcinoma (HCC) for Bulgarian patients.

2 Material and methods

Methodology

The prospective, cross-sectional study was conducted over a 24 month period (January 2022 to December 2024) among newly diagnosed patients with viral hepatitis B and C in Bulgaria. The survey took place at the University hospital "Aleksandrovska" in Sofia, one of the centers responsible for diagnosing, treating, and monitoring patients suffered from hepatitis.

The study included a total of 140 patients, where 76 patients have hepatitis B (HBV) and 64 have hepatitis C (HCV). Patients were examined during their first visit to the hospital. The inclusion criteria for HCV hepatitis were: availability of positive anti-HCV antibodies with detectable viral load by polymerase chain reaction (PCR) and no signs of ascites. The inclusion criteria for HBV hepatitis were availability of positive HBsAg and positive or negative HBeAg. DNA $>$2000 IU/mL detected by PCR. Patients' demographic and clinical characteristics (virus load, blood characteristics, liver stiffness) were collected. The patients were divided according to type of hepatitis and age into subgroups.

The liver stiffness of patients (LS) was evaluated in all patients by means of FibroScan 430 mini, trademarks of Echosens Company, France as a standard care for patients with hepatitis (Fig. 1). The mean values of liver stiffness were calculated for every group and subgroups of patients.

Fig. 1. Fibroscan used to assess the liver stiffness of patients.

For the purposes of the study a serum marker FIB-4 which includes platelet count, aspartate aminotransferase-to platelet radio index was calculated (eq. 1) for HBV and HCV patients [24, 25].

$$\mathrm{FIB}-4 = (\mathrm{age} \times \mathrm{AST})/(\mathrm{platelet\ count} \times (\mathrm{ALT})^{1/2}) . \tag{1}$$

STATISTICS

The following statistical methods were used to analyze the data: descriptive statistics provided baseline characteristics (mean age, number of patients with high and low level of stiffness, percent of patients with severe fibrosis),parametric tests such as the t-test was used to compare the difference between age in subgroups, the mean values of liver stiffness for group B and C. Chi-square test was applied to the proportions of patients with a certain level of fibrosis in order to compare the proportions.

Correlation analyses was applied to present the correlation between LS and age for patients with hepatitis B or C. Logistic regression analysis was used to calculate odds ratios (OR) according to age and type of hepatitis. In order to calculate odds ratio we grouped results for high level of stiffness (stage F3-F4) before and after 50 years and compared with low level of stiffness (stage F0–F1) before and after 50 years for hepatitis B and C. FIB-4 and LS were used to predict the development of the hepatitis. Serum marker FIB-4 were calculated using platelet count, aspartate aminotransferase-to platelet radio index for every patient and eq. (1). MedCalc software (version 22.014) was used for data analysis.

ETHICS

All patients newly diagnosed with viral hepatitis B and C at the Hospital for active treatment "Aleksandrovska" in Sofia were invited to participate in the study. Participation was entirely voluntary. Each patient gave their informed consent to use their anonymized data for scientific research purposes and fill a declaration for participation. The study was approved by the decision N:7/ 2023 of the Ethical Committee of the Medical University of Sofia.

3 RESULTS

The mean age of HBV patients is 50.76±11.81 years while mean age of HCV is 49.89±13.48 yrs. The smallest age in the sample was 19 years, and the largest – 82 years. The difference between age is not statistically significant ($p = 0.659$). The relationship between age and LS for both type of hepatitis are presented in Figs. 2 and 3. Liver stiffness of HCV patients changes up to 25 kPa while liver stiffness for HBV patients grows to 16 kPa. The trend is positive and 12.24% of values of liver stiffness for HCV are above maximum value of LS for HBV – 16 kPa.

Mean values of LS for HCV patients are 9.87 ±8.19 kPa and are higher than values of LC for HBV patient 7.96±3.84 kPa). Comparison of mean values of liver stiffness for group B and C showed that there is no statistical significance between them (p=0.31).

Distribution of liver elasticity according to age and stage of fibrosis for both types

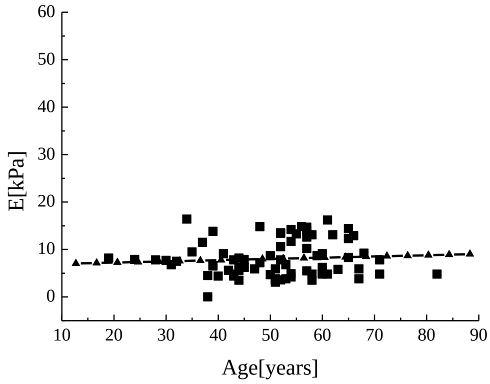

Fig. 2. Correlation between LS and age for patients with hepatitis B.

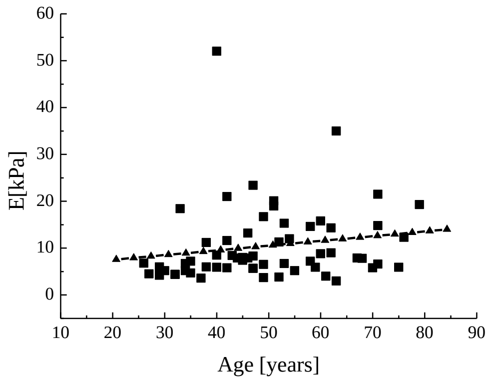

Fig. 3. Correlation between LS and age for patients with hepatitis C.

of hepatitis is presented in Table 1. The results showed that in case of HVB the values of LS for subgroup over 50 yrs are higher than the values of LS for under 50 yrs (8.44±4.08 kPa vs 7.41±3.32 kPa). The same trend was obtained for HCV(10.78 ±7.52 kPa vs 9.59±8.94 kPa). The results are not statistically significant.

Table 1. Liver elasticity according to age and fibrosis stage F0-F4

	Median LS [kPa]	LS under 50 yrs	LS over 50 yrs	F0-F1 [%]	F2 [%]	F3 [%]	F4 [%]
HBV	7.35	7.41±3.32	8.44±4.08	48.68	23.68	25	2.63
HCV	7.8	9.59±8.94	10.78±7.52	42.8	20.63	14.29	15.8

The median value for liver elasticity in both groups is similar. Evaluating the level of liver damage we obtained that the majority of patients have low level of fibrosis stage F0-F1 (48.7% for HBV vs 42.8% for HCV) followed by middle level F2 (23.7% vs 20.6%). The level of fibrosis F3 is higher for HBV (25%) than for HCV – 14.3%. Stage F4 (cirrhosis) is predominant in the group of HCV patients – 15.8% (Table 1). The Chi-square test demonstrated that the overall proportions of patients with a certain level of fibrosis were comparable in both groups of hepatitis except stage F4 ($p < 0.05$). The comparison of mean values of LS according to fibrosis stages showed linear increase (not shown). For stage F4 the values of liver stiffness for two type of hepatitis are statistically significant ($\mathrm{LS} = 2.55 \pm 2.96$ vs 20.86 ± 10.76, $p = 0.013$).

Table 2 presents the results for odds ratio according to age and hepatitis. Hepatitis C and age over 50 leads to high level of stiffness. According to Sporea and Sirli [16] the cut-off values for severe fibrosis is an Young modulus in the interval [9.5–13 to

Table 2. Logistic regression results

Determinant	High level of stiffness (N)	Low level of stiffness (N)	OR, 95% CI, p
			OR = 1.24
HCV	19	27	95%CI [0.56-2.74]
HBV	21	37	$p = 0.53$
Age, HBV			OR = 2.16
$>$ 50 years	17	22	95%CI [0.65-7.19]
20-49 years	5	14	$p = 0.208$
Age, HCV			OR = 3.25
$>$ 50 years	13	9	95% CI [0.98-10.68]
20-49 years	8	18	$p = 0.052$

15 kPa] and over 15 kPa the patient suffers from liver cirrhosis. The mean values of Young modulus for cirrhotic patients is 26.5±11.1 kPa according to Guibal et al. which means that lower limit is again 15 kPa [26].

Table 3 presents the percent of patients with severe fibrosis. The patients in risk are those whose liver stiffness is over 13 kPa and their part is significant 18–25%. Percent of patients with severe fibrosis and suspected carcinoma are higher in case of HCV. The results are statistically significant when LS is greater than 15 kPa ($p < 0.05$).

Table 3. Percent of patients with severe fibrosis

Type of hepatitis	LS over13kPa	LS over 15 kPa	LS over 30 kPa
HBV	18.2%	2.6%	NA
HCV	25.4%	19.5%	3.17%
p value	$p > 0.05$	$p < 0.05$	

The calculated mean value of FIB-4 for HCV is 2.36±2.52 (median 1.44) and for HBV patients is 1.64±1.28(median 1.22).

4 Discussion

There are many methods to assess and predict liver disease – blood tests, biopsy or noninvasive methods using medical devices. Today is possible to investigate also blood rheological properties like whole blood viscosity, plasma viscosity, RBC (red blood cel) deformability, RBC aggregation, or platelet aggregation and procoagulant activity. The alteration of these parameters are connected with development of cancer and can be used to monitoring the process [27, 28].

In this study we decide to use ultrasound based transient elastography as the most validated elastographic technique today in order to assess the expectable levels of hepatocellular carcinoma (HCC) in the cohort of Bulgarian patients.

A liver cancer risk among patients with chronic viral hepatitis is higher in older people and those with severe liver fibrosis [29]. This was the reason to divide the patients into two subgroups – before and after 50 yrs and to calculate the odds ratio of cancer development.

The main results from the study show that the level of liver damage in case of HBV and HCV is low because the initial level of fibrosis stage F0-F1 is 48.7% for patients with HBV vs 42.8% for patients with HCV. The level of fibrosis F3 is higher for patients with HBV (25%) than for those with HCV – 14.3%, while cirrhosis is predominant in the group of HCV patients – 15.8% (Table 1). The values of LS according to age showed linear increase in case of HCV (Fig. 3). For stage F4 the values of liver stiffness for hepatitis C are significant higher than the values of for hepatitis B (20.86±10.76 vs. 12.55±2.96).

The cut-off value of LS for healthy Bulgarian patients is up to 5.5 [kPa] [20]. This imposed the conclusion that patients at risk with hepatitis C have 4 or 5 times higher values of LS while patients at risk with hepatitis B have 2–2.5 times higher values of LS than normal values. The presence of a low correlation between age and a Fibroscan data is not unusual because there are many factors that have a predictive value for non-invasive determination of liver fibrosis: liver density, FIB-4, decreased platelet counts, elevated AST, age, elevated GGT(gamma-glutamyl transferase), body weight, elevated triglycerides ALT, cholesterol [20]. Obviously age is not the most important factor.

It was obtained that between 18-25% of patients are with severe fibrosis. This highlighted the need of monitoring in order to prevent cancer incidence among this patients.The percent of HBV patients with LS greater than 15 kPa is only 2.6% which means that the chance for carcinoma is low but about 20% from HCV patients have a risk for carcinoma. According to logistic regression the patients over 50 yrs have 3.25 times higher odds of increased LS compared to those under 50 in case of HCV and 2.15 times higher odds in case of HBV.

The correlation between liver stiffness measured by TE and the risk of developing HCC has been reported by a large prospective Japanese study [30]. The authors reported increased cumulative incidence of HCC within 3 years – 38.5% among patients with baseline liver stiffness values greater than 25 kPa, compared with 0.4% among patients with values less than 10 kPa [30].

Yada et al. published prospective risk analysis of hepatocellular carcinoma in patients with chronic hepatitis C by ultrasound strain elastography [31]. The cumulative liver cancer incidences for years 1, 2, 3, 4, and 5 were, for the entire cohort: 2.0%, 5.6%, 8.8%, 13.1%, and 23.9% [31].

HCC can be affected by hepatic inflammation, obesity, ascites, cholestasis (for all elastographic methods), and steatosis (for transient elastography) which means that is not recommendable to use liver stiffness measurement as unique predictor of HCC [8]. The authors connected liver fibrosis index FIB-4 with cancer incidents. When FIB-4 $\leq$ 2.0 there is no cases of cancer. For those whose FIB-4 was in the interval 2–2.8 the incidence was between 0.0% and 19.9%. If the values of FIB-4 were greater than 2.8 the incidence increase to 12.9% after first year and 31.4% after fifth year [31].

The results for FIB-4 greater than 2.8 for our cohort are 16.88% for HBV group of patients and 23.44% for HCV group of patients. The percent of patients with liver stiffness over 13 kPa are 18.2% and 25.4% (See Table 3). It can be supposed that this serum marker predict well the level of patients in risk.

The study has some limitations. There is no a control group of patients which results to compare with the results of the patients with viral hepatitis and the data from the literature was used. We investigated only the influence of age and liver elasticity on the chance of hepatocellular carcinoma development. The correlation between risk of cancer and other factors should be revealed in the the next study.

5 Conclusions

Accurate staging of liver fibrosis is necessary in establishing prognosis. Transient elastography is an accurate tool for diagnosing liver fibrosis and cirrhosis in a wide range of etiologies. Liver stiffness measured by transient elastography and FIB-4 index should be used in the diagnosis of advanced stages of liver fibrosis in patients with viral hepatitis B and C. According to our results 20% from HCV patients and 3% from HBV patients might have a risk of hepatocellular carcinoma. The long term monitoring of those patients should be performed to validate the prognosis.

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