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ПРИЛОЗИ. Одд. за мед. науки, XLV 3, 2024 МАНУ
CONTRIBUTIONS. Sec. of Med. Sci., XLV 3, 2024 MASA

10.2478/prilozi-2024-0026 ISSN 1857-9345

CORRELATION BETWEEN REAL-TIME SHEAR WAVE ELASTOGRAPHY AND LIVER SERUM MARKERS IN DETERMINING THE STAGE OF LIVER FIBROSIS IN PATIENTS WITH CHRONIC LIVER DISEASES

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ABSTRACT

Introduction: Non-invasive methods aim to predict the stage of liver fibrosis in line with histological findings via biopsy. Shear wave elastography and serum markers are proven as accurate non-invasive methods for determining liver fibrosis as a modern non-invasive methods compared to liver biopsy in staging hepatic fibrosis.

Aims: This study aims to determine the correlation between Shear Wave Elastography and indirect and direct serum markers of fibrosis when staging liver fibrosis.

Material and methods: The study was conducted in the Clinic of Gastroenterohepatology, the Institute of Immunology and Human Genetics, and the Institute of Pathology between 2021 and 2023. The study comprises 70 patients with liver lesions, diagnosed based on clinical results, laboratory tests, and ultrasound imaging. All patients underwent liver biopsy, classified according to Ishak and Metavir score as a reference method for diagnosing liver fibrosis. Real-time shear wave elastography was also performed as a non-invasive method and serum markers were checked for liver fibrosis.

Findings: The statistical analysis indicated a positive correlation between the values of direct and indirect liver fibrosis markers and Shear Wave Elastography results.

Conclusion: Our study has demonstrated that shear wave elastography has a significant positive correlation with biochemical markers of liver lesions and serum markers of liver fibrosis, whereas it has a negative correlation with platelets.

Keywords: Liver fibrosis, direct and indirect markers of liver fibrosis, Shear wave elastography, liver biopsy (Ishak and Metavir classification)

INTRODUCTION

Liver fibrosis represents the histological consequence of the so called “healing process” in various chronic liver diseases of various etiology. There are two main types of cells in the liver, such as the parenchymal cells (70-85% of the liver parenchyma) and non-parenchymal cells [1]. Liver stellate cells are non-parenchymal cells which reside in the subendothelial space of Disse between hepatocytes and sinusoidal endothelial cells and are the main source of the extracellular matrix in a normal fibrotic liver. In normal liver parenchyma, there is a balance between the synthesis and the breakdown of components of the extracellular matrix [2]. When fibrosis occurs, significant qualitative and quantitative changes in the extracellular matrix happen. The process of the development of liver fibrosis lasts from several months up to several years (except for the disease of vein occlusion, mechanic biliary obstruction,

and fibrosing cholestatic hepatitis whereby due to unknown reasons fibrosis can progress rapidly.

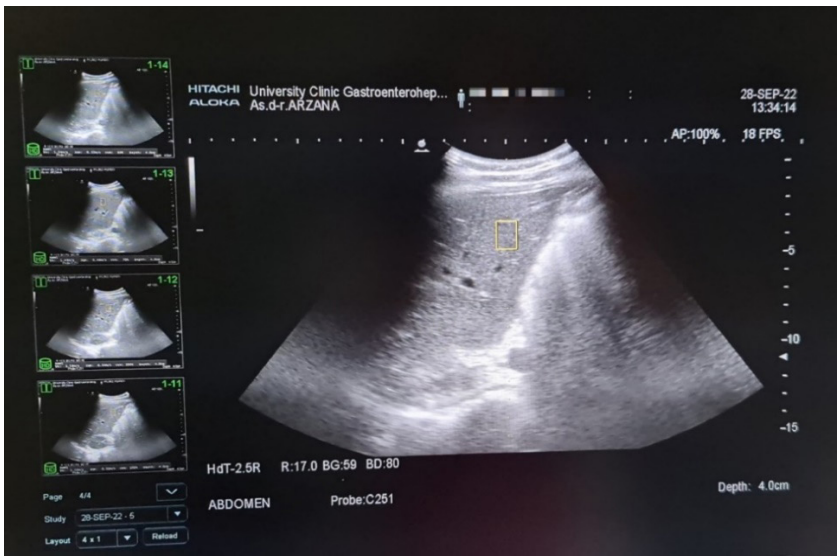
Fibrosis detection is essential in the evaluation and treatment of patients with chronic liver lesions. The methods used for examining liver fibrosis are divided into non-invasive and invasive methods (liver biopsy). Non-invasive methods aim to predict the stage of liver fibrosis in line with histological findings via biopsy. Different serum markers were evaluated for predicting the stage of liver fibrosis, and panels were developed (a combination of several markers), and they aim to differentiate patients without fibrosis (F0 and F1) from those with significant fibrosis (F2 and F4).

Serum markers of liver fibrosis are divided into indirect and direct markers. Indirect markers of liver fibrosis (platelets, coagulation factors, aminotransferase) reflect alterations in the function of the liver, but they do not directly reflect the metabolism of the extracellular matrix. Direct markers for liver fibrosis directly reflect the metabolism of the extracellular matrix (procollagen type 3 and type 1, hyaluronic acid, and tissue inhibitor of metalloproteinase). In our study at the Institute of Immunology and Human Genetics, the concentration of direct serological markers of liver fibrosis, namely, procollagen type III amino-terminal peptide (PIIINP), collagen type IV, laminin and hyaluronic acid, was examined using the chemiluminescent method. Procollagen type III amino terminal peptide (PIIINP) – is one of the main components of the extracellular matrix whose concentration increases during the process of fibrogenesis when there is a liver lesion. In 1979, Rojking et al. discovered that in a cirrhotic liver, serum markers have increased values by 4 up to 7 times [3] PIIINP values are increased in acute and chronic liver diseases, and they correlate with serum markers in serum values of aminotransferase in patients with active hepatitis and with serum values of bilirubin in patients with liver cirrhosis. Serum type IV collagen correlates to the stage of fibrosis in patients with alcoholic liver disease, hemochromatosis, and HCV infection, and values are increased in patients with chronic liver disease. A study of patients with chronic hepatitis indicated that type IV collagen is more sensitive than laminin, hyaluronic acid, and procollagen type 3 amino-terminal peptide in staging liver fibrosis [4–9]. Laminin (LN) is a non-collagenous glycoprotein, synthesized by hepatic stellate cells and deposited in the basement membrane of the liver up to the moment when the liver lesion occurs, then it is deposited around blood vessels and perisinusoidal spaces and portal tracts [10,11]. Laminin values correlate with the stage of liver fibrosis, i.e. the values increase in patients with cirrhosis and portal hypertension as well as other complications of cirrhosis [12–17]. Alcohol abstinence decreases laminin values, but values do not normalize in response to antiviral therapy in patients with HCV infection [18–20]. Hyaluronic acid (HA) is among the most studied direct biomarkers and was discovered by Mayer and Palmer in the vitreous of the eyes of cows in 1934. In the same year, it was first used in ophthalmology. Hyaluronic acid has various functions in many cellular processes in the body such as angiogenesis, cancer processes and metastases, inflammation, and the immune system. HA is a glycosaminoglycan synthesized by hepatic stellate cells, degraded by sinusoidal cells, and is a component of the extracellular matrix [21]. Hyaluronic acid is produced by activated hepatic stellate cells and is a main component of the extracellular matrix. In a damaged liver, an increased concentration of HA in serum is observed due to increased synthesis and targeted elimination through the damaged liver. Hyaluronic acid values in the serum have the highest predictive accuracy for advanced fibrosis, that is, they are increased when the function of endothelial sinusoidal cells is disturbed in advanced fibrosis, that is, cirrhosis of the liver of different etiology [22].

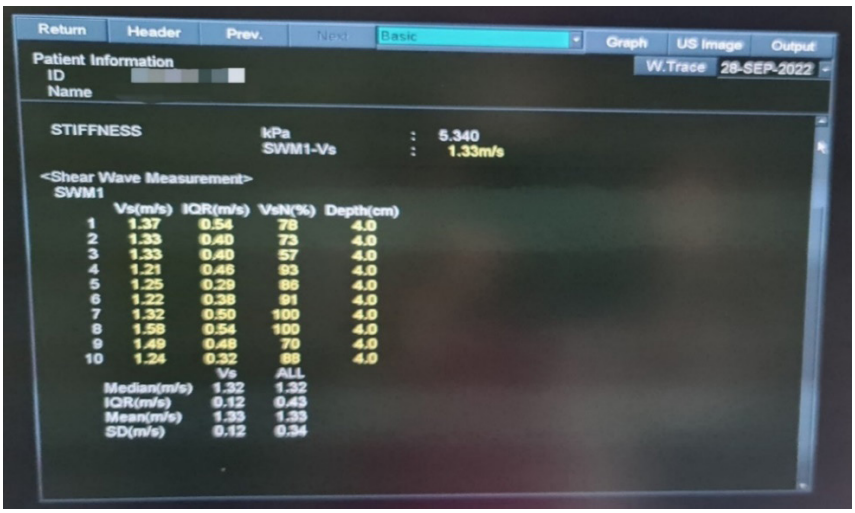
Ultrasound elastography is a modern imaging method analogous to tissue palpation when palpable stiffness is usually a sign of disease. Elastography methods are used in clinical practice as additional methods that help to increase the specificity of the diagnosis of many diseases. The history of ultrasound elastography dates from the early 1980s. The name and the method were used for the first time by Ophir and his colleagues in 1991. The method is based on the fact that different biological tissues have different elasticity and that changes in elastic properties are often associated with tissue abnormality. The essence of the method is the examination of tissue response to low-frequency vibrations and the amplitude caused by the transducer of the ultrasound device. The measurement of the elasticity of the tissue is based on the speed of the shear wave movement through the tissue, as well as the density of the tissue through which the wave passes, hence the speed of the movement of the wave is higher when it passes through tissue with greater density, that is, stiffness. With regards to the liver, the method is used to stage liver fibrosis. There are several

methods for performing shear wave elastography such as Transient elastography or Fibroscan, [23–26] Point shear wave elastography [27,28], and 2D shear wave elastography [29–31]. The methods differ according to the method of generating the shear waves, as well as the surface of the liver parenchyma where the measurements of those waves are made (in point elastography, the measurements are made from a smaller area of the liver (5-10 mm) or in 2D-SWE sequential measurement from multiple areas of the liver). Shear wave techniques (transient elastography and ARFI) measure the speed of movement of shear waves through the tissue and they convert it in KiloPascal, a unit of Yang module.

In our clinic, the method was introduced in 2017 and it is Real-time elastography and Shear wave measurement (SWM). The device that was used was Arietta V70 Hitachi Aloca with a convex C251(1.8-5.0MHz) probe. Real-time elastography is a two-dimensional method that measures the elasticity of the tissue during examination. Integrated into the Hitachi device, shear wave measurement (SWM) software measures the speed of wave propagation through the tissue, thus determining liver elasticity. The method lasts from 15 to 30 minutes. The result is automatic, and it represents a mean value calculated from 10 consecutive measurements of the speed of wave movement through the tissue (Vs), with a quality index that expresses the percentage of efficient measurement (VsN) which cannot be under 50%. (Picture 1 and Picture 2).



Picture 1. E*xample of performing elastography in the right lobe of the liver. Example of correct placement of the region of interest during elastography*



Picture 2. *Display of results when measuring liver fibrosis with Shear Wave Elastography*

The result provides staging of fibrosis, ranging from F0 to F4, and is expressed as one of several modules of elasticity expressed in kilopascal (kPa) or shear wave speed m/s depending on whether tissue elasticity is measured or the speed of wave movement across the tissue. When the value is 5.8 kPa or lower (4.4-5.5kPa), there is no liver fibrosis (F0), the liver is healthy and when the value is over 9.6 kPa there is an expressed fibrosis F4, i.e., cirrhosis. (Table 1) The measurement is performed according to the recommendations of the European Federation of Societies for Ultrasound in Medicine and Biology - EFSUMB.

Table 1. *Reference values from the measurements with shear wave elastography for staging liver fibrosis in patients with chronic viral hepatitis [32]*

Stages of fibrosis	Shear Wave Measurement-SWM (IQR)
Mild fibrosis (F0-F1)	4.99 (3.94-5.98)
Moderate fibrosis (F≥2)	7.84 (6.22-10.02)
Severe fibrosis (F≥3)	8.85 (7.41-9.59)
Liver cirrhosis (F=4)	13.84 (12.62-16.59)

When performing this method, to obtain more exact results, one must avoid measuring near the blood vessels, in the depth of the liver, in the corners of the liver, but also positioning the region of interest for elastography <1.5 cm from the liver capsule. Real-time shear wave elastography is not performed in obese patients with narrow intercostal spaces, patients with ascites, patients with congestive heart disease, postprandially, and during deep inhalation during the intervention.

Liver biopsy is an invasive procedure, whereby a small sample is taken from the liver for histopathological diagnosis and for staging various liver diseases. There are three types of liver biopsy, such as: percutaneous, laparoscopic, and transvenous [33]. In everyday practice, percutaneous biopsy is usually used. In our study, samples of liver biopsy taken from 70 patients were analyzed at the Institute of Pathology and the stage of liver fibrosis was determined by the histopathologist according to the Ishak classification expressed in 6 scores, as well as the Metavir classification expressed in 5 scores. The biopsy is embedded in paraffin. Histological sections were stained with Hematoxylin & Eosin (HE) and histochemical Trichrome Azan for evaluation of liver fibrosis. The results were analyzed, photographed, and documented with a NIKON 80i light microscope. The histological evaluation of the sample obtained from the liver is the basis for evaluation and determination of the type of lesion, but also the basis for planning the treatment of patients with liver disease. Histological scoring systems for chronic liver disease are used to predict the progression of the disease, as well as the treatment of patients with chronic liver disease. The most popular systems are Knodell, METAVIR, and Ishak score. Other less important systems are Scheuer, Batts-Ludwig, and Laennec [34]. The difference between the scoring systems lies in the stage of fibrosis. According to Knodell's classification, the result divides patients into one of four stages. According to the METAVIR classification, the result divides patients into one of five stages (table 2). The systems that comprise more stages of fibrosis may reveal even the small changes in fibrosis over time. The newest Ishak scoring system divides patients into one of six stages. Metavir scoring is a semi-quantitative classification system that is composed of fibrosis results and the stage of the activity. The score is designed for patients with HCV infection. The limitations of the Metavir scoring are similar to the Knodell scoring, i.e., the result varies depending on the sample taken by the physician who has performed the biopsy and the interpretation of results by a hepatologist.

Table 2. *Metavir scoring (Fibrosis and the stage of necroinflammatory activity) [35]*

Stages of fibrosis		Stage of necro-inflammatory activity	
No fibrosis	F0	No activity	A0
Portal fibrosis without septa	F1	Mild activity	A1
Portal fibrosis with few septa	F2	Moderate activity	A2
Portal fibrosis with numerous septa without cirrhosis	F3	Severe activity	A3
Cirrhosis	F4		

Ishak scoring (modified Knodell scoring) - Ishak scoring comprises six stages of fibrosis which display even the smallest changes when there are lesions of the liver parenchyma of different etiology (table 3). Same as Metavir scoring, the results of necroinflammatory activity and liver fibrosis are displayed separately.

Table 3. *Ishak scoring (changes in the structure, of the liver parenchyma, fibrosis, and cirrhosis) [36]*

Changes in the structure of the liver	scoring
No fibrosis	0
Fibrous expansion of some portal areas, with or without short fibrous septa	1
Fibrous expansion of most portal areas, with or without short fibrous septa	2
Fibrous expansion of most portal areas with occasional portal-to-portal bridging	3
Fibrous expansion of most portal areas with marked bridging, portal to portal as well as portal to central	4
Marked bridging with occasional nodules (incomplete cirrhosis)	5
Cirrhosis, probable or definite	6

In recent years, Ishak scoring has become widely used in clinical examinations, especially in the United States of America. Since each stage of fibrosis in Ishak scoring reflects multiple septa from the previous phase, researchers presume that the transition from one stage to another represents progressive and more advanced liver disease, but this has not yet been confirmed [37] [36]. In terms of fibrosis, Ishak and Metavir are almost identical. Ishak scoring has a wider scale with 6 points (table 4).

Table 4. *Comparison between Ishak and Metavir, histopathological staging of liver fibrosis [38]*

Ishak scoring	Metavir scoring
(0) No fibrosis	F0 (No fibrosis)
(1) Mild fibrosis	F1 (mild to moderate fibrosis)
(2) Mild – moderate fibrosis	Between F1 and F2
(3) Moderate fibrosis	F2 (Moderate fibrosis)
(4) Moderate to severe fibrosis	F3 (Severe fibrosis)
(5) Incomplete cirrhosis	Between F3 and F4
(6) Cirrhosis	F4 (Cirrhosis)

In line with the current literature, in our study, the stage of fibrosis is pathohistologically determined according to Ishak and Metavir scoring.

AIMS

This study aims to determine the correlation between Shear Wave Elastography and indirect and direct serum markers of fibrosis when staging liver fibrosis.

MATERIALS AND METHODS

For the aims of this study, a prospective study was carried out in the Clinic of Gastroenterohepatology, the Institute of Immunology and Human Genetics, and the Institute of Pathology, in the period from 2021-2023. The study comprised 70 patients ranging from 18 to 80 years of age, hospitalized in the Clinic of Gastroenterohepatology, diagnosed with liver lesions based on previous clinical, biochemical tests, and ultrasound. The study does not comprise obese patients, patients with cardiopulmonary diseases, with ascites, and with malignant disease. Patients were divided into 5 groups: Patients with persistent hepatitis, aggressive hepatitis, liver steatosis, steatofibrosis, and cirrhosis. All patients underwent Real-time Shear Wave Elastography, and liver biopsy classified according to Metavir and Ishak, and direct and indirect markers of liver fibrosis were also examined.

STATISTICAL ANALYSIS

The statistical analysis of the data from the study was made with the statistical program SPSS 23.0. Kolmogorov-Smirnov test and Shapiro Wilk's test were used for testing the distribution of data. The data received is displayed in tables and charts. Categorical (attributive) variables are displayed with absolute and relative numbers. Numerical (quantitative) variables are displayed with median, standard deviation, minimal and maximal values, median value, and interquartile range. To compare the groups with different stages of liver fibrosis and the different diagnoses of liver diseases, concerning categorical variables, non-parametric tests were used for independent samples (Chi-square test, Fisher exact test), and concerning quantitative variables, parametric and non-parametric tests were

used for comparing independent samples, depending on the symmetry of the data (Analysis of Variance, Kruskal-Wallis test, Mann-Whitney test). For examining the correlation between the stages of hepatic fibrosis with serum markers, and between SW Elastography with serum markers, Pearson's coefficient of linear correlation and Spearman's coefficient of rank correlation were used depending on the symmetry of the data. The statistical significance was defined in the level p<0.05.

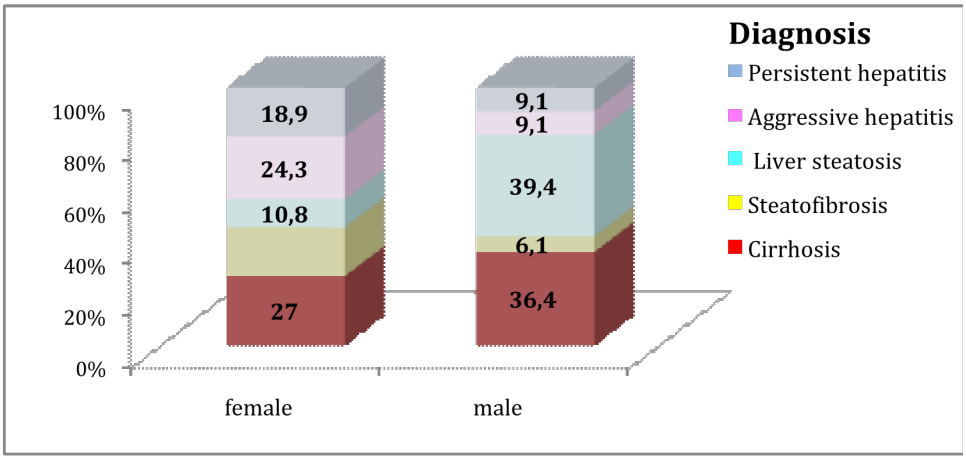
RESULTS

70 patients participated in this study, all from the clinic of Gastroenterohepatology with diagnosed liver lesions. The sex structure of patients was as follows: 37 (52.86%) of patients were male and 33 (47.14%) were female patients. The age of patients ranged from 18 to 75, with a mean age of 52.4±12.7 years. According

Table 5. *Sex distribution of patients according to the type of liver disease*

Diagnosis	Sex		p – value
	female = 37 n (%)	male = 33 n (%)	
Persistent hepatits	7 (18.9)	3 (9.1)	Fisher's exact test *p=0.017
Aggressive hepatitis	9 (24.3)	3 (9.1)	
Liver steatosis	4 (10.8)	13 (39.4)	
Steatofibrosis	7 (18.9)	2 (6.1)	
Cirrhosis	10 (27.0)	12 (36.4)	

*p<0.05



Picture 3. *Graphic display of sex distribution of patients according to the type of liver disease*

Table 6. *Age of patients according to the type of liver disease*

Age years	Diagnosis				
	Persistent hepatitis	Aggressive hepatitis	Liver steatosis	Steatofibrosis	Cirrhosis
n	10	12	17	9	22
mean ± SD	42.3 ± 13.8	57.8 ± 9.7	50.6 ± 12.6	52.6 ± 13.3	55.4 ± 11.5
min – max	18 – 64	35 – 71	29 – 72	32 – 75	35 – 75
Analysis of Variance test F=2.8 *p=0.033 Post-hoc Tukey honest test: intergroup differences for age					
Persistent hepatitis		*0.03	0.43	0.36	*0.045
Aggressive hepatitis			0.51	0.86	0.98
Liver steatosis				0.99	0.72
Steatofibrosis					0.97

F(Analysis of Variance)

to the diagnosis the study comprised 10 patients with persistent hepatitis, 12 patients with aggressive hepatitis, 17 patients with liver steatosis, 9 patients with steatofibrosis, and 22 patients with cirrhosis. Female and male patients demonstrated significant differences concerning the diagnosis of the liver lesion (p=0.017). In female patients, the most common diagnosis was cirrhosis – 10 (27%), followed by aggressive hepatitis – 9(24.3%); while in male patients the most common diagnosis was cirrhosis – 12(36.4%), followed by steatosis – 13(39.4%). Hepatitis and steatofibrosis were most common in female patients, and steatosis and cirrhosis were more common in male patients. (Table 5, Picture 3)

Patients with aggressive hepatitis were the oldest, with an average age of 57.8 ± 9.7, followed by patients with cirrhosis with an average age of 55.4 ± 11.5, patients with steatofibrosis with an average age of 52.6 ± 13.3, patients with steatosis with an average age of 50.6 ± 12.6, and youngest were the patients with persistent hepatitis with an average age of 42.3 ± 13.8. (Table 6)

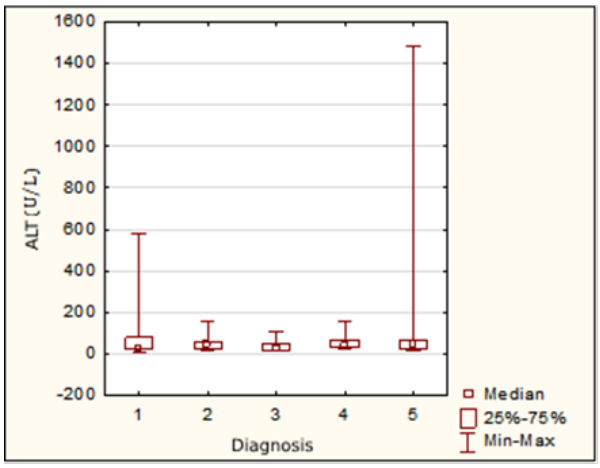
Patients with hepatitis, steatosis, steatofibrosis, and cirrhosis had significantly different values of AST (p=0.0014). Post-hoc analysis for intergroup comparisons demonstrated that this statistical significance is due to the significantly higher values of AST in patients with cirrhosis in relation to patients with liver steatosis (p=0.00036). Average values of AST in the groups with persistent hepatitis, aggressive hepatitis, steatosis, steatofibrosis, and cirrhosis are 76.10 ± 133.2U/L, 43.17 ± 19.5 U/L, 27.87 ± 13.7 U/L, 47.40 ± 25.1 U/L and 117.23 ± 189.2 U/L, respectively (table 7).

Patients with persistent and aggressive hepatitis, steatosis, steatofibrosis and cirrhosis did not differ significantly in terms of ALT values (p=0.46).

Platelets had an average value of 204.30 ± 27.7, 230.92 ± 96.9, 243.47 ± 86.6, 280.11 ± 116.9, 173.0 ± 69.6 109/L, accordingly in the

Table 7. *Value of AST according to the type of liver disease*

AST (U/L)	**Diagnosis**				
	Persistent hepatitis	Aggressive hepatitis	Liver steatosis	Steatofibrosis	Cirrhosis
n	10	12	17	9	22
mean ± SD	76.10 ± 133.2	43.17 ± 19.5	27.87 ± 13.7	47.40 ± 25.1	117.23 ± 189.2
median (IQR)	29.5 (20 – 44)	38 (27.5 – 62)	22 (20 – 30)	42.63 (28 – 61)	53 (34 – 109)
Kruskal-Wallis test H=17.7 **p=0.0014 Post-hoc Mann-Whitney test: intergroup differences in ACT					
Persistent hepatitis		1.0	1.0	1.0	0.36
Aggressive hepatitis			0.36	1.0	1.0
Liver steatosis				0.37	**0.00036
Steatofibrosis					1.0



Picture 4. *Median values of ALT according to the liver disease*

groups with persistent hepatitis, aggressive hepatitis, steatosis, steatofibrosis and cirrhosis. (Table 8, Picture 5). Platelet counts differed significantly depending on the diagnosis (p=0.0125). With regards to the inter-group differences, with the post-hoc analysis, we could detect statistical significance between the groups with steatofibrosis and cirrhosis. Patients with fibrosis had significantly lower platelet counts. (Table 8)

Patients with persistent hepatitis, aggressive hepatitis, steatosis, steatofibrosis, and cirrhosis did not differ significantly concerning the values of bilirubin (p=0.36) (Table 9, Picture 6).

Prothrombin time was insignificantly different according to the diagnosis (p=0.635). The average value of prothrombin time was 12.30 ± 1.5, 12.0 ± 1.1, 12.3 ± 2.5, 11.8 ± 0.9 и12.7 ± 1.5 seconds, adequately to the groups with persistent hepatitis, aggressive hepatitis, steatosis, steatofibrosis, and cirrhosis (Table 10, Picture 7).

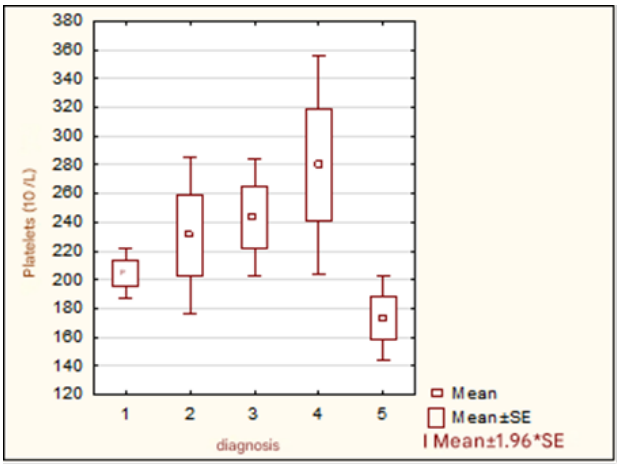
Prothrombin index was highest in the group of patients with cirrhosis (1.08 ± 0.1), followed by the group of aggressive hepatitis (1.11 ± 0.3), the groups with persistent hepatitis and steatosis (1.05 ± 0.3), lowest were in the group with steatofibrosis (0.97 ± 0.1). The tested difference of the prothrombin index between the groups did not differ statistically (p=0.66) (Table 11, Picture 8).

Average and median values of procollagen III amino peptide serum marker were 71.31 ± 121.8 and 15.28 ng/mL, accordingly in the group with persistent hepatitis, 60.62 ± 89.0 and 17.6 ng/mL, accordingly in the group with aggressive hepatitis, 47.37 ± 44.1 and 23.6 ng/mL, accordingly in the group with steatosis, 35.57 ± 56.1 and 12.9 ng/mL, accordingly in the group with steatofibrosis, and 174.49 ± 200.7 and 59.05 ng/mL, accordingly in the group with cirrhosis (Picture 9). Concerning p=0.0049 the overall statistically significant difference in the values of PIIINP was confirmed, depending on the type of

Table 8. *Platelet count according to the type of liver disease*

PLT (10^9/L)	Diagnosis				
	Persistent hepatitis	Aggressive hepatitis	Liver steatosis	Steatofibrosis	Cirrhosis
n	10	12	17	9	22
mean ± SD	204.30 ± 27.7	230.92 ± 96.9	243.47 ± 86.6	280.11 ± 116.9	173.0 ± 69.6
min – max	161 – 248	77 – 407	127 – 494	183 – 508	64 – 312
Analysis of Variance test F=3.5 *p=0.0125 Post-hoc Tukey honest test: intergroup differences in PLT					
Persistent hepatitis		0.9	0.75	0.28	0.86
Aggressive hepatitis			0.1	0.66	0.3
Liver steatosis				0.82	0.073
Steatofibrosis					*0.014

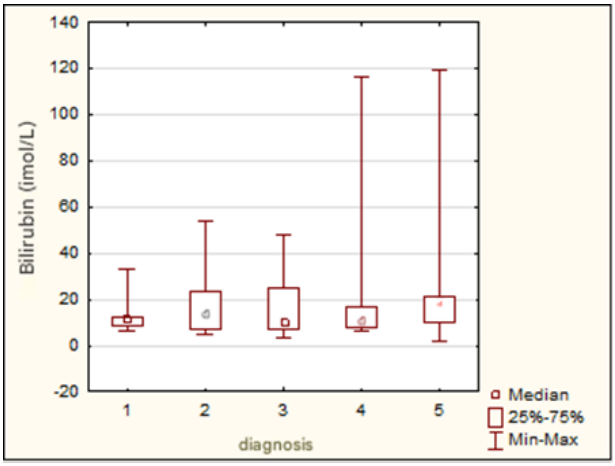
F(Analysis of Variance)
*p<0.05



Picture 5. A*verage platelets count according to the type of liver disease*

Table 9. Bilirubin values according to the type of liver disease

Bilirubin (umol/L)	**Diagnosis**				
	Persistent hepatitis	Aggressive hepatitis	Liver steatosis	Steatofibrosis	Cirrhosis
n	10	12	17	9	22
mean ± SD	12.80 ± 7.5	17.87 ± 14.6	15.95 ± 13.6	22.92 ± 35.2	28.55 ± 34.6
median (IQR)	11.3 (8.8 – 12.4)	13.05 (7.15 – 23.1)	9.8 (6.8 – 24.6)	10.4 (7.9 – 16.9)	17.9 (9.8 – 21.5)
p – value	H=4.3 p=0.36				

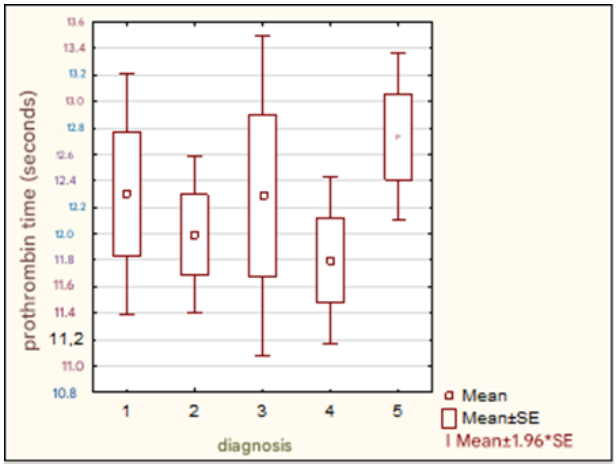


Picture 6. *Median values of bilirubin according to the type of liver disease*

Table 10. *Deviation of values of prothrombin time according to the type of liver disease*

PT (sek.)	**Diagnosis**				
	hepatits persistens	hepatitis agressiva	steatosis	Steatofibrosis	cirrhosis
n	10	12	17	9	22
mean ± SD	12.3 ± 1.5	12.0 ± 1.1	12.3 ± 2.5	11.8 ± 0.9	12.7 ± 1.5
min – max	10 – 15	10.6 – 13.4	10 – 20.4	10.7 – 13.8	10.1 – 17.3
p – value	F=0.6 p=0.635				

F(Analysis of Variance)

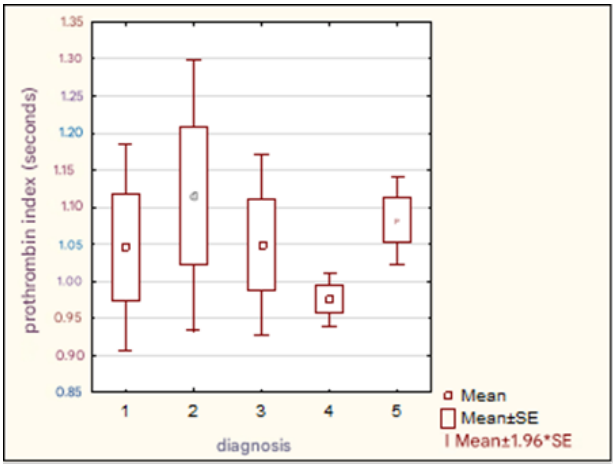


Picture 7. *Average value of prothrombin time according to the type of liver disease*

Table 11. *Values of the prothrombin index according to the type of liver disease*

INR (sek.)	Diagnosis				
	Persistent hepatitis	Aggressive hepatitis	Liver steatosis	Steatofibrosis	Cirrhosis
n	10	12	17	9	22
mean ± SD	1.05 ± 0.2	1.11 ± 0.3	1.05 ± 0.3	0.97 ± 0.1	1.08 ± 0.1
min – max	0.59 – 1.4	0.9 – 2.1	0.83 – 1.83	0.9 – 1.09	0.84 – 1.52
p – value	F=0.6 p=0.66				

F(Analysis of Variance)

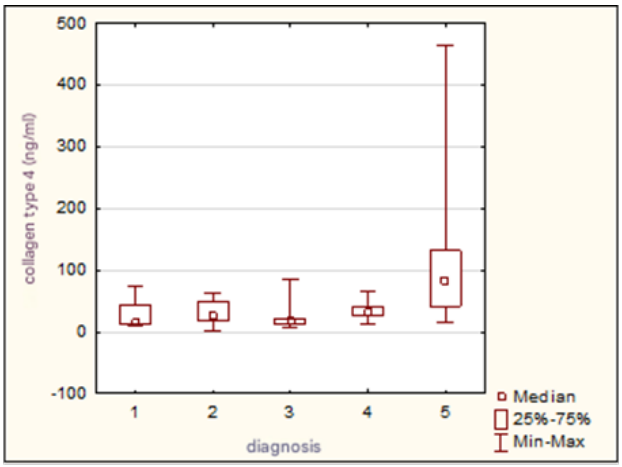


Picture 8. *Average value of INR according to the type of liver disease*

Table 12. *Collagen type 4 values according to the type of liver disease*

Collagen type IV (ng/ml)	**Diagnosis**				
	Persistent hepatitis	Aggressive hepatitis	Liver steatosis	Steatofibrosis	Cirrhosis
n	10	12	17	9	22
mean ± SD	28.03 ± 25.9	31.59 ± 18.9	21.22 ± 18.4	35.56 ± 18.9	125.01 ± 126.1
median (IQR)	13.71 (13.2 – 41.9)	26.05 (17.25 – 48.04)	15.5 (11.91 – 21.4)	31.8 (26.2 – 41.2)	83.65 (41.6 – 131)
Kruskal-Wallis test H=30.74 ***p=0.00000 post-hoc Mann-Whtney test; intergroup differences in collagen type 4					
Persistent hepatitis		1.0	1.0	1.0	***0.0009
Aggressive hepatitis			1.0	1.0	**0.038
Liver steatosis				1.0	***0.000004
Liver steatofibrosis					0.12

H(Kruskal-Wallis test) **p<0.001,***p<0.0001



Picture 10. *Median values of collagen type 4 according to the type of liver disease*

liver disease, which confirmed with the post-hoc analysis that it is due to the high values of PIINP in the group with cirrhosis compared to the groups with persistent hepatitis and steatofibrosis (p=0.039, p=0.019, accordingly).

Collagen type 4 serum marker presented average values of 13.53± 5.4 ng/ml, 27.99 ± 23.1 ng/ml, 27.77 ± 19.2 ng/ml, 47.78 ± 12.5 ng/ml and 133.62 ± 129.3 ng/ml, accordingly in the groups F0, F1, F2, F3 and F4 stage of liver fibrosis; the median of values of collagen type 4 was 12.05 ng/ml, 17.9 ng/ml, 20.1 ng/ml, 49.7 ng/ml and 85.6 ng/ml, accordingly in the groups F0, F1, F2, F3 and F4 stage of liver fibrosis (Table 12, Picture 10). There was a statistical significance in the values of collagen type 4 depending on the type of liver disease (p<0.0001).Post-hoc analysis for inter-group comparisons indicated that patients with cirrhosis had a significantly higher collagen type 4 compared to patients with persistent hepatitis (p=0.0009), patients with aggressive hepatitis (p=0.038), and in relation to patients with steatosis (p=0.000004) (Table 12).

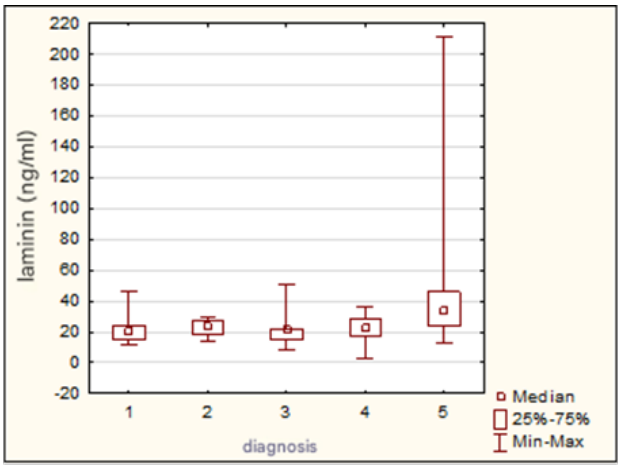
Laminin had average values of 22.31 ± 10.6 ng/mL, 22.51 ± 5.2 ng/mL, 22.08 ± 10.9 ng/mL, 21.97 ± 10.9 ng/mL and 44.88 ± 42.3 ng/mL, accordingly in the groups with persistent hepatitis, aggressive hepatitis, steatosis, steatofibrosis, and cirrhosis; the median of laminin values was 20.45 ng/mL, 23.05 ng/mL, 20.8 ng/mL, 22.3 ng/mL and 33.5 ng/mL, accordingly in the groups with persistent hepatitis, aggressive hepatitis, steatosis, steatofibrosis and cirrhosis (Table 13, Picture 11). For p=0.0059 a general statistically significant difference of laminin between the groups was confirmed, which is due to the significantly higher values of laminin in patients with cirrhosis, in relation to patients with liver steatosis (post-hoc, p=0.008) (Table 13).

Among the groups with persistent hepatitis, aggressive hepatitis, steatosis, steatofibrosis, and cirrhosis, the general statistically significant difference of hyaluronic acid was confirmed (p=0.001). The post-hoc analysis confirmed that this significance is due to the significantly higher values of this serum marker in the group with cirrhosis compared to the group with persistent

Table 13. *Laminin values according to the type of liver disease*

Laminin (ng/ml)	**Diagnosis**				
	Persistent hepatitis	Agressive hepatitis	Liver steatosis	Steatofibrosis	Cirrhosis
N	10	12	17	9	22
mean ± SD	22.31 ± 10.6	22.51 ± 5.2	22.08 ± 10.9	21.97 ± 10.9	44.88 ± 42.3
median (IQR)	20.45 (14.6 – 24.41)	23.05 (18 – 26.85)	20.8 (15.1 – 22.2)	22.3 (17.5 – 28.7)	33.5 (23.5 – 45.8)
Kruskal-Wallis test H=14.5 **p=0.0059 post-hoc Mann-Whtney test: intergroup differences in Laminin					
Persistent hepatitis		1.00	1.00	1.00	0.0799
Aggressive hepatitis			1.00	1.00	0.2046
Liver Steatosis				1.00	0.008
Steatofibrosis					0.3304

H(Kruskal-Wallis test)
*p<0.05, **p<0.01

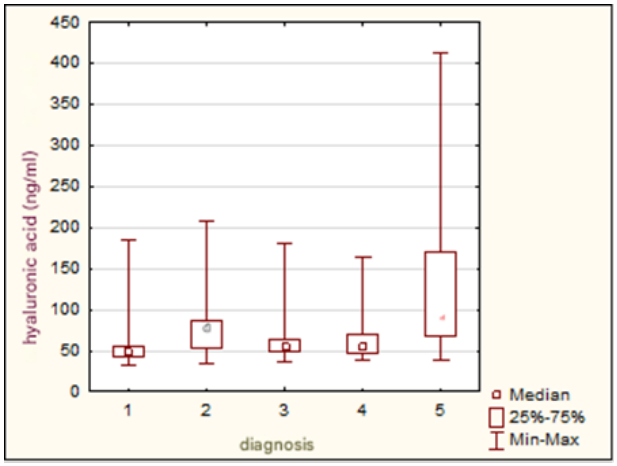


Picture 11. *Average laminin values according to the type of liver disease*

Table 14. Deviation of hyaluronic acid values according to the type of liver disease

Hyaluronic acid (ng/ml)	Diagnosis				
	Persistent hepatitis	Aggressive hepatitis	Liver steatosis	Steatofibrosis	Cirrhosis
n	10	12	17	9	22
mean ± SD	60.38 ± 44.1	83.43 ± 47.7	61.28 ± 31.8	67.64 ± 38.3	129.84 ± 95.9
median (IQR)	48.1 (41.7 – 54.8)	76.24 (53.7 – 86.1)	53.9 (48.9 – 63.4)	54.8 (47.5 – 69.2)	90.45 (68 – 170)
Kruskal-Wallis test H=18.5 **p=0.001 post-hoc Mann-Whtney test: intergroup differences in hyaluronic acid					
Persistent hepatits		0.35	1.0	1.0	**0.0035
Aggressive hepatitis			1.0	1.0	1.0
Liver steatosis				1.0	*0.01
Steatofibrosis					0.161

H(Kruskal-Wallis test)
*p<0.05, ***p<0.01



Picture 12. *Median values of hyaluronic acid according to the type of liver disease*

hepatitis (p=0.0035) and in relation to the group with steatosis (p=0.01). (Table 14) Average and median values of hyaluronic acid were highest in the group with cirrhosis (129.84 ± 95.9 and 90.45 ng/mL, accordingly), followed by the groups with aggressive hepatitis (83.43 ± 47.7 and 76.24 ng/mL, accordingly), steatofibrosis (67.64 ± 38.3 and 54.8 ng/mL, accordingly), steatosis (61.28 ± 31.8 and 53.9 ng/mL, accordingly) and persistent hepatitis (60.38 ± 44.1 and 48.1 ng/mL, accordingly) (Table 14, Picture 12).

In line with the results of the statistical analysis, the values of shear wave elastography in the groups with persistent hepatitis, aggressive hepatitis, liver steatosis, steatofibrosis and cirrhosis were significantly different (p<0.0001). Post-hoc analysis which served to make inter-group comparisons demonstrated that this general significant difference is due to the significantly higher values of elastography in the group with cirrhosis compared to other groups (p=0.00013), there were significantly higher values in the group with aggressive hepatitis compared to the group with steatosis (p=0.0074), and significantly higher values in the group with steatofibrosis compared to the group with steatosis (p=0.022). (Table 15) Average values of elastography were highest in the group with cirrhosis (13.76 ± 2.5 KPa), lowest in the group with steatosis (4.97 ± 0.9KPa). Average values in the group with hepatitis (persistent and aggressive) and with steatofibrosis were 6.63 ± 1.7, 7.63 ± 2.4 and 7.57 ± 1.8 KPa, accordingly. (Table 15, Picture 13)

This study analyses the correlation of the non-invasive method with elastography and with the stage of liver fibrosis determined with Metavir and Ishak scoring. All analyzed direct and indirect markers of liver fibrosis (except for ALT), significantly correlated to Metavir and

Ishak scoring ($p<0.05$, $p<0.01$, $p<0.0001$). In line with the values of Spearman coefficient, the correlation with platelets was negative, while the correlation with all other parameters was positive. These statistical results indicate that more advanced stages of liver fibrosis are related to lower platelets, higher values of AST, bilirubin, prothrombin time, prothrombin index, procollagen III amino peptide, collagen type 4, laminin, hyaluronic acid and higher values of elastography, and vice versa (Table 16,17).

There was no significant correlation between the age of patients with elastography ($p=0.22$). There was no significant correlation between the elastography and ALT, bilirubin, and prothrombin time ($p=0.7$, $p=0.35$ and $p=0.15$, accordingly) (Table 17).

Elastography showed a significantly positive correlation with AST ($R=0.308$, $p=0.009$), prothrombin index ($R=0.247$, $p=0.039$), PIIINP ($R=0.306$, $p=0.001$), collagen type 4($R=0.6-9$, $p<0.0001$), laminin ($R=0.361$, $p=0.002$) and hyaluronic acid ($R=0.507$, $p=0.00001$), while there was a significant negative correlation with platelets ($r= -0.322$, $p=0.006$). (Table 18) By increasing AST, INR, PIIINP, collagen type 4, laminin, and hyaluronic acid, and by decreasing the number of platelets, the value of elastography is increased and vice versa (Table 18, Picture 14,15,16,17,18,19,20).

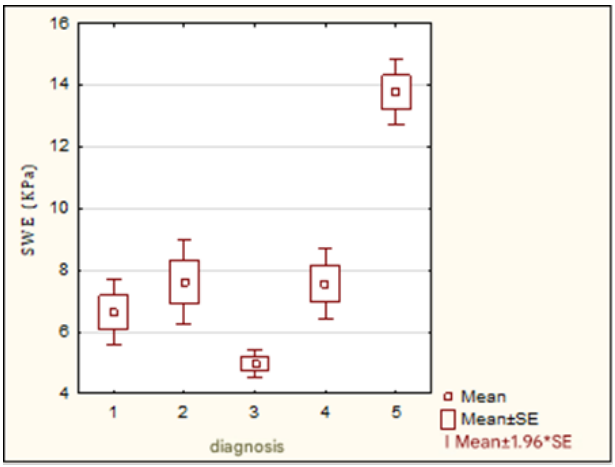
DISCUSSION

The main reason for liver fibrosis in industrialized countries is chronic infection with the Hepatitis C virus, alcohol abuse, and non-alcoholic steatohepatitis (NASH), which are becoming more prevalent around the world and in our country with high morbidity and mortality. The prognosis and adequate and immediate treatment in chronic liver diseases depend largely on the stage of liver fibrosis. Especially in patients with

Table 15. *Elastography values according to the type of liver disease*

SWE (KPa)	**Diagnosis**				
	Persistent hepatits	Aggressive hepatitis	Liver steatosis	Steatofibrosis	Cirrhosis
N	10	12	17	9	22
mean ± SD	6.63 ± 1.7	7.63 ± 2.4	4.97 ± 0.9	7.57 ± 1.8	13.76 ± 2.5
min – max	4.5 – 9.9	3.98 – 11.98	3.2 – 6.31	3.98 – 9.46	8.75 – 17.98
Analysis of Variance test F=53.2 ***p=0.000 post-hoc Tukey honest test: intergroup differences in SWE					
hepatits persistens		0.8	0.25	0.84	***0.00013
hepatitis aggressive			**0.0074	1.0	***0.00013
Liver steatosis				*0.022	***0.00013
Steatofibrosis					***0.00013

F(Analysis of Variance)
*p<0.05,**p<0.01, ***p<0.0001



Picture 13. *Average elastography values according to the type of liver disease*

Table 16. *Correlation of Metavir score with age, elastography, and serum markers for fibrosis*

Correlation		
METAVIR SCORE	Spearman R	p – value
age	0.193	0.14
AST (U/L)	0.469	***0.00004
ALT	0.164	0.17
PLT (10^9/L)	-0.362	**0.002
Bilirubin (umol/L)	0.276	*0.021
PT (sek.)	0.283	*0.0178
INR (sek.)	0.281	*0.0189
PIIINP	0.339	**0.004
Collagen type 4 (ng/ml)	0.699	***0.000000
Laminin (ng/ml)	0.403	***0.00054
Hyaluronic acid (ng/ml)	0.509	***0.000007
SWE (KPa)	0.871	***0.000000

*p<0.01, **p<0.01, ***p<0.0001

Table 17. *Correlation of Ishak score with age, elastography, and serum markers for fibrosis*

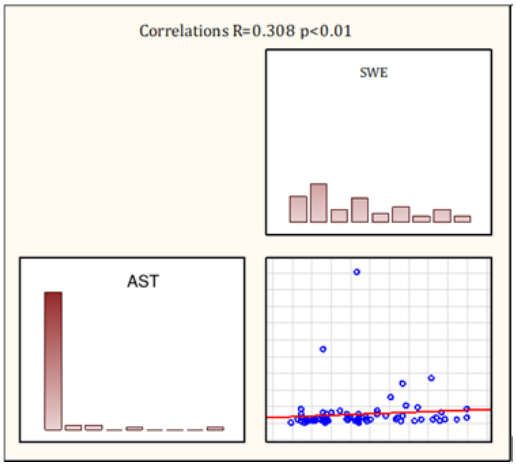
Correlation		
ISHAK SCORE	Spearman R	p – value
Age	0.160	0.295
AST (U/L)	0.439	***0.00014
ALT (U/L)	0.101	0.4
PLT (10^9/L)	-0.369	**0.0017
Bilirubin (umol/L)	0.264	*0.027
PT (sek.)	0.341	**0.0039
INR (sek.)	0.334	**0.0047
PIIINP	0.329	**0.0053
Collagen type 4 (ng/ml)	0.692	***0.00000
Laminin (ng/ml)	0.416	***0.00034
Hyaluronic acid (ng/ml)	0.507	***0.00001
SWE (KPa)	0.932	***0.00000

*p<0.01, **p<0.01, ***p<0.0001

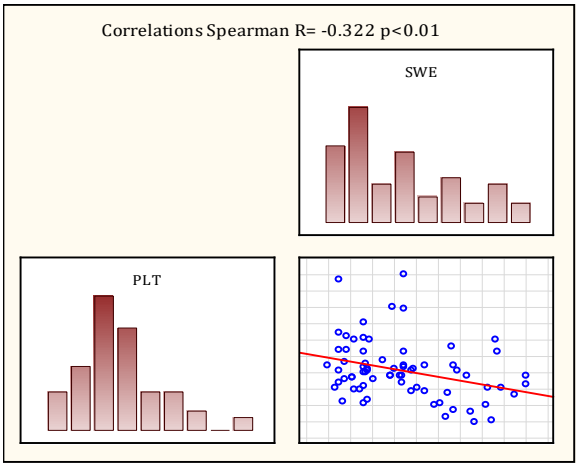
Table 18. *Correlation of elastography with age and serum markers of fibrosis*

	Correlation		
SWE	Spearman R	Pearson r	p – value
Age		0.173	0.22
AST (U/L)	0.308		**0.009
ALT (U/L)	0.047		0.7
Bilirubin	0.114		0.35
PLT (10^9/L)		-0.322	**0.006
PT		0.173	0.15
INR (sek.)	0.247		*0.039
PIIINP	0.306		**0.001
Collagen type 4 (ng/ml)	0.609		***0.00000
Laminin(ng/ml)	0.361		**0.002
Hyaluronic acid (ng/ml)	0.507		***0.00001

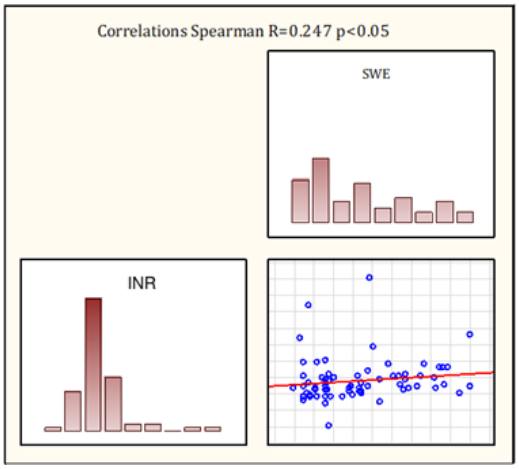
*p<0.05, **p<0.01, ***p<0.0001



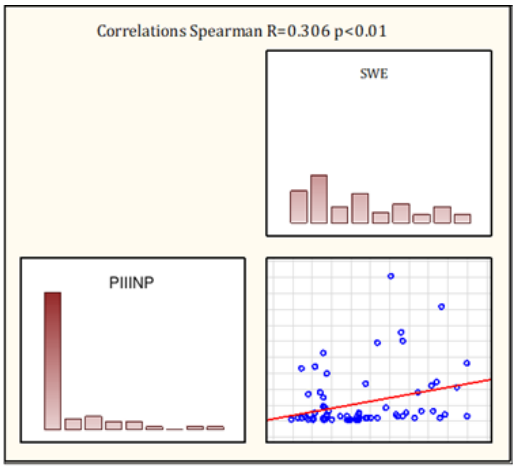
Picture 14. *Correlation - elastography with AST*



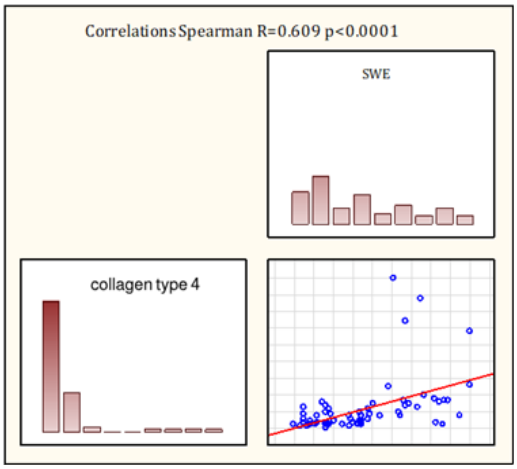
Picture 15. *Correlation - elastography with PLT*



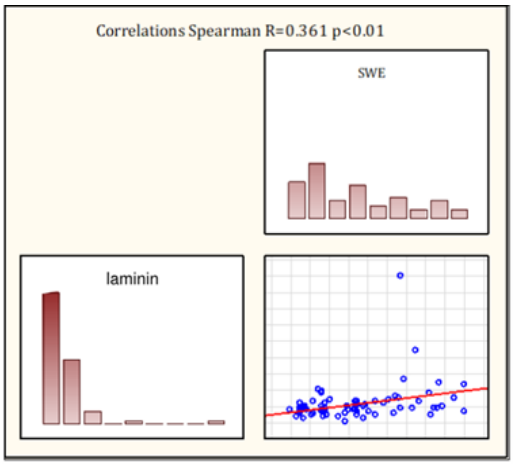
Picture 16. *Correlation - elastography with INR*



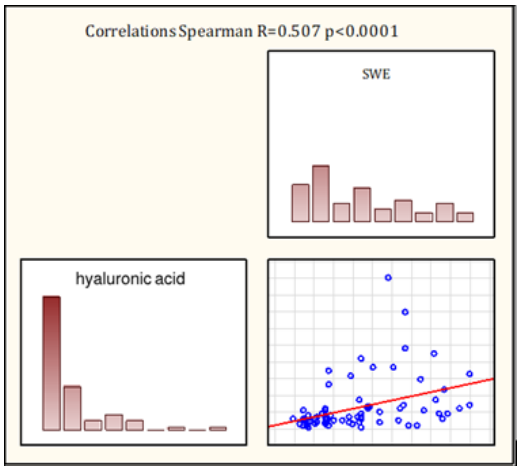
Picture 17. *Correlation - elastography with PIIINP*



Picture 18. *Correlation – elastography with collagen type 4*



Picture 19. *Correlation - elastography with laminin*



Picture 20. *Correlation - elastography with hyaluronic acid*

hepatitis B and C, staging fibrosis plays a major role in disease monitoring and therapeutic interventions. Although liver biopsy is still the gold standard in staging hepatic fibrosis, three decades ago a group of scientists focused on discovering and perfecting non-invasive methods, to avoid the complications of invasive methods that were used continuously. Elastography, as a new ultrasound technique, uses ultrasound rays, produced in the transducer of the device (during the examination of the patient) to induce mechanical vibrations that diverge toward the tissue. This ultrasound technique undertakes quantitative mechanic vibrations and by using Young's formula, it transforms them and expresses them in an elasticity index in kilopascals. Liver fibrosis is also measured by direct measurement of tissue elasticity. Normal liver tissue is more elastic, and the values are lower compared to fibrotic tissue caused by various liver diseases [39]. In our study, elastography values were highest in patients with cirrhosis (13.76 ± 2.5 KPa), and lowest in patients with liver steatosis (4.97 ± 0.9kPa). Average values in the group with hepatitis (persistent and aggressive) and with steatofibrosis were 6.63 ± 1.7, 7.63 ± 2.4 and 7.57 ± 1.8 kPa, accordingly. The difference in the type of the device, the type of elastography technique, and the experience of the operator working with the method also the accuracy of Metavir scoring may be the reason for different results for all fibrosis stages, especially for F4 fibrosis stage. The study of Ferrailli et al. indicated that the mean value of tissue stiffness in the stage of cirrhosis was 15kPa, while the study of Guibal et al. indicated a value of 25.8kPa, whereas our study indicated a value of 13.7kPa [40]. As far as we are informed, there is a limited number of studies examining the correlation of Shear Wave Elastography with biochemical analysis of liver function, and most of them are contradictory and they refer to other elastography techniques, i.e., to transient elastography [41]. The study of Cebula et al. [42] demonstrated a high correlation of SWE with two biochemical parameters (AST and INP) as fibrotest. Bota et al. had similar results [43]. The study of Gharibvand et al. indicated that there is a direct and significant correlation between the elasticity of liver tissue in various stages of fibrosis with the values of AST and ALT. The highest values of ALT and AST are found in F3 stage of fibrosis and lowest values were found in F0. Our study confirmed the statistically significant difference in the distribution of patients with elevated and normal AST values, depending on the stage of liver fibrosis. AST values in patients with F3 and F4 stage of fibrosis compared to patients with F0 were significantly higher and these values were significantly higher in patients with F3 compared to patients with F1. Patients with hepatitis, liver steatosis, steatofibrosis, and cirrhosis had no significant differences in relation to ALT values. All liver lesions cause a reduced number of hepatocytes, which causes hyperbilirubinemia. Correct mechanisms of the relation between bilirubin and fibrotic progression are hard to determine. We can assume that bilirubin can cause cytotoxic effects, an im-

balance of the redox homeostasis, and finally apoptosis. On the other hand, the activated hepatic stellate cells that store retinoids may contribute to an increased level of direct bilirubin in the blood, or the elevated bilirubin may cause a stress response to the endoplasmic reticulum resulting in reduced proliferative and metabolic activity of hepatocytes [44]. The study of Du et al. indicated significant differences in the values of serum bilirubin between individuals with or without HCV infection. Higher values of serum bilirubin were noted in most advanced fibrosis or cirrhosis in a larger group of workers with HCV infection. In the study of Shu et al., which focused on the value of direct bilirubin in a group of adults, in non-obese patients with and without NAFLD, no correlation was detected between the levels of serum bilirubin and the prevalence of NAFLD [45]. The study of Zhou et al. indicated a correlation of elastography values with the values of direct and indirect bilirubin in 40 newborns with biliary atresia [46]. In our study, high bilirubin value was detected in one patient with persistent hepatitis, 3 patients with aggressive hepatitis, 5 patients with steatosis, one patient with steatofibrosis and 7 patients with cirrhosis, without statistical significance between them. The liver not only has the functions of detoxification and inactivation, anabolism, and excretion of bile, but it is also the main organ in the body for the synthesis and inactivation of various coagulation factors, prothrombin, and antithrombin, which are essential to maintain the balance between the system for coagulation and anticoagulation system. Cirrhosis, i.e. the advanced stage of liver fibrosis, is characterized by degeneration and necrosis of hepatocytes, which leads to the synthesis of a series of coagulation factors and a reduced ability to clean thromboactive enzymes and activating fibrinolytic factor, which results in a decrease in the coagulation and anticoagulation function of the body. The study of Peng et al., which compared the function parameters, platelets, and factors, coagulation indices between the two groups, namely the healthy group and those with cirrhosis, proved that they all effectively reflect liver lesion, among which the coagulation indices do not provide a basis for early diagnosis of patients with cirrhosis [47]. In our study, the correlation between prothrombin time and the index and the stage of liver fibrosis had an insignificantly different value between the groups with different diagnoses. Values were only increased in patients with cirrhosis and in patients with hepatitis and liver steatofibrosis. Platelets were present in many processes of hepatic fibrosis. According to some studies, platelets may reduce the expression of TGF -beta and may increase the expression of matrix metalloproteinase in the process of liver fibrosis. Thrombocytopenia, which is common in patients with chronic liver disease and cirrhosis, is thought to result from decreased production of thrombopoietin and platelet destruction caused by hypersplenism (the relationship between thrombocytopenia and the pathogenesis of liver disease, as well as the role of platelets in chronic liver disease). Kurokawa et al. proved that platelets affect the improvement of liver fibrosis by reducing the production of collagen by stellate cells [48]. This explains the regenerative effect of the liver after transfusion with platelets in patients with chronic liver disease and liver cirrhosis. The study by Zhong et al., proved as the stage of liver fibrosis advances, the value of platelets decreases, so that in F0 the values of platelets are higher compared to cirrhosis where there is thrombocytopenia. The results of our study are similar to the study of Li et al [49]. In the prospective study of Xie et al. in which patients with liver cirrhosis of viral etiology (HBV positive) were examined, a combined algorithm of 2D elastography and the value of platelets was carried out, whereby better prognosis of complications and of varicose hemorrhage was achieved in patients with liver cirrhosis [50]. Patients with F0, F1, F2, F3, and F4 stages of liver fibrosis had significantly different values of platelets ($p=0.0053$). Group F0 registered a significantly higher platelet count compared to the groups F2 and F3. In this study, platelet count was significantly different depending on the diagnosis, i.e., patients with cirrhosis had significantly lower platelet counts. Only two patients had platelet counts above normal, 1 with steatosis and 2 with steatofibrosis. In contrast to indirect markers of liver fibrosis previously described, direct markers of liver fibrosis reflect directly the function of the extracellular matrix. In addition to elastography as a non-invasive method, 4 direct serum markers for liver fibrosis were analyzed in the study. In our study as well as in various studies around the world, a correlation between serum markers of fibrosis and the stage of liver fibrosis has been demonstrated. In a retrospective study by Jeong et al., which comprised patients with liver damage of different etiology, a correlation of serum markers for fibrosis with the stage of

liver fibrosis was found, but not with the value of elastography, i.e. elastography correlates better with the stage of fibrosis compared to serum markers for liver fibrosis [51]. The study of Wang et al., comprised 137 newborns with cholestasis (biliary atresia, choledochal cyst, or cytomegaloviral hepatitis), in the period between 2016-2019, with histopathological analysis of hepatic biopsy according to Metavir scoring and with examined serum markers of liver fibrosis. From the obtained results, no correlation of procollagen type 3 amino-terminal peptide and hyaluronic acid with the stage of liver fibrosis, especially with cirrhosis, was proven. No significant correlation of laminin with the stage of liver fibrosis has been demonstrated [52]. A retrospective study by Mei et al. included 791 patients with compensated cirrhosis divided into three groups, without esophageal varices, initial esophageal varices, and endoscopically proven developed esophageal varices. The obtained results revealed a positive correlation between serum markers of liver fibrosis and initial esophageal varices, especially increased laminin values in first-stage esophageal varices in compensated liver cirrhosis [53]. Our study confirmed the difference in increased values of PIIINP depending on the type of liver disease. Thus, patients with cirrhosis often have an elevated serum marker for PIIINP followed by patients with liver steatosis, aggressive hepatitis, steatofibrosis, and persistent hepatitis. It has also been confirmed that there is a difference depending on the stage of liver fibrosis. PIIINP values are higher in the F4 group compared to F2. Collagen type 4 values were highest in patients with cirrhosis, followed by patients with persistent hepatitis, aggressive hepatitis, and liver steatosis. It has also been confirmed that there is a significant difference in collagen values depending on the stage of fibrosis. The values are higher in the group of F4 compared to F0, F1, and F2 as well as significantly higher values in the group of F3 compared to F0. It was confirmed that there is a statistically significant difference in laminin between the groups, with higher values in patients with cirrhosis compared to patients with steatosis. Patients with F4 hepatic fibrosis have higher laminin values than patients with F0 and F2. Hyaluronic acid significantly differs in different stages of hepatic fibrosis, the values are higher in F4, F3, F2, F0 and F1. Regarding the disease, higher values of hyaluronic acid were confirmed in patients with cirrhosis compared to the group with persistent hepatitis and the group with steatosis.

CONCLUSION

Our study analyzed the correlation of indirect and direct markers of liver fibrosis with shear wave elastography in staging liver fibrosis. Regarding the diagnoses (persistent and aggressive hepatitis, liver steatosis, and steatofibrosis as well as cirrhosis), the value of elastography differs significantly. According to the obtained results, the elastography values do not significantly depend on sex and age of the patients. In our study, the results indicate that more advanced stages of liver fibrosis are related to lower platelet count, higher values of AST, bilirubin, prothrombin time, prothrombin index, procollagen III amino peptide, collagen type 4, laminin, hyaluronic acid and higher values of elastography, and vice versa. A statistically significant difference was detected in the finding of increased values of PIIINP among the different stages of liver fibrosis. A significant difference of PIIINP values was confirmed, depending on the type of liver disease. Statistically significant was the difference in collagen type 4 values depending on the stage of fibrosis and in relation to the etiology of the disease, which is due to a significantly higher type 4 collagen in the F4 group, compared to F0, F1 and F2, as well as significantly higher collagen type 4 in group F3 compared to F0. In patients with cirrhosis, the values are higher than in patients with persistent hepatitis, aggressive hepatitis, and liver steatosis. The mean and median values of the serum marker laminin were highest in the F4 group and lowest in the F0 group. In relation to the etiology, it was confirmed that there is a statistically significant difference in laminin between the groups, with higher values in patients with cirrhosis compared to patients with steatosis. A statistically significant difference was detected in the finding of increased values of hyaluronic acid among different stages of liver fibrosis, as well as in relation to the different etiology of the disease. In our study, no statistically significant difference was detected in the frequency of ALT, bilirubin, prothrombin time and prothrombin index values. Patients with hepatitis, liver steatosis, steatofibrosis, and cirrhosis had significantly different AST values, that is, AST values are sig-

nificantly higher in patients with cirrhosis compared to patients with liver steatosis. We found a statistically significant difference in the distribution of patients with elevated and normal AST values depending on the stage of liver fibrosis. The group F0 registered a significantly higher platelet count compared to F2 and F3. Our study has demonstrated that shear wave elastography has a significantly positive correlation with biochemical markers of liver lesion and serum markers of liver fibrosis, whereas it has a negative correlation with platelets. The results of our research showed that elastography as a modern non-invasive method together with biochemical and serum markers for liver fibrosis correlate with the results of liver biopsy in staging liver fibrosis obtained according to Metavir and Ishak classification. We hope that in the future more sophisticated elastography methods will be used, we hope for a study with a larger group of patients with liver lesion with fewer limitations in the selection of patients as well as fewer limitations in performing the method itself. We expect that in the future non-invasive methods will be the only methods for diagnosing liver diseases of various etiology.

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Резиме

КОРЕЛАЦИЈА МЕЃУ REAL TIME SHEAR WAVE ЕЛАСТОГРАФИЈА И ЦРНОДРОБНИТЕ СЕРУМСКИ МАРКЕРИ ВО ОДРЕДУВАЊЕ НА СТАДИУМОТ НА ФИБРОЗА НА ЦРНИОТ ДРОБ КАЈ ПАЦИЕНТИ СО ХРОНИЧНИ ЗАБОЛУВАЊА НА ЦРНИОТ ДРОБ

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Вовед: Неинвазивните методи имаат цел да го предвидат стадиумот на хепатална фиброза во согласност со хистолошкиот наод добиен со биопсија. Shear wave еластографијата, заедно со одредувањето на серумските маркери за фиброза на црнниот дроб како неинвазивни модерни методи се докажани како прецизен метод во однос на хепатална биопсија во одредувањето на степенот на хепатална фиброза.

Цели: Целта на овој труд е да се утврди корелацијата меѓу еластографијата Shear Wave и серумските индиректни и директни маркери на фиброза во одредувањето на степенот на црнодробната фиброза.

Материјали и методи: Студијата е изведена на Клиниката за гастроентерохепатологија, Институтот за имунологија и хумана генетика и Институтот за иатологија во период од 2021 до 2023 година. Во студијата се вклучени 70 пациенти со црнодробна оштета, дијагностицирана врз основа на клиничката слика, лабораториските анализи и улатрасонографскиот наод. Кај сите пациенти е изведена хепатална биопсија класифицирана според скорот Ишак и Метавир, како референтна метода за дијагноза на хепаталната фиброза на црниот дроб, изведена е неинвазивната метода Real time shear wave еластографија и се испитани серумските маркери за фиброза на црниот дроб.

Резултати: Статистичка анализа покажа позитивна корелација меѓу вредностите на директните и на индиректните маркери за фиброза на црниот дроб и резултатие од еластографијата Shear wave.

Заклучок: Во нашата студија е докажано дека еластографијата shear wave значително позитивно корелира со биохемиските маркери на црнодробната лезија и серумските маркери на фиброзата на црниот дроб, додека негативно корелира со тромбоцитите.

Клучни зборови: хепатална фиброза, директни и индиректни маркери за фиброза на црниот дроб, Shear wave еластографија, хепатална биопсија (класификација Ишак и Метавир)