



The Role and Significance of Non-invasive Methods, with a Particular Focus on Shear Wave Elastography in Hepatic Fibrosis Staging

Arzana Hasani Jusufi*, Meri Trajkovska¹, Rozalinda Popova-Jovanovska², Viktorija Calovska-Ivanova³, Atip Ramadani, Vladimir Andreevski⁴

Clinic of Gastroenterohepatology, Ss. Cyril and Methodius University of Skopje, Skopje, Republic of Macedonia

Abstract

Edited by: Ksenija Bogoeva-Kostovska
Citation: Jusufi AH, Trajkovska M, Popova-Jovanovska R, Calovska-Ivanova V, Ramadani A, Andreevski V. The Role and Significance of Non-invasive Methods, with a Particular Focus on Shear Wave Elastography in Hepatic Fibrosis Staging. Open Access Maced J Med Sci. 2022 Apr 14; 10(B):1607-1614. <https://doi.org/10.3889/oamjms.2022.9048>

Keywords: Liver/hepatic fibrosis; Diffuse liver disease; Shear wave elastography; Serum markers of liver fibrosis

*Correspondence: Arzana Hasani Jusufi, Clinic of Gastroenterohepatology, Ss. Cyril and Methodius University, Skopje, Republic of Macedonia.
E-mail: zanahassani65@gmail.com

Received: 20-Feb-2022

Revised: 02-Apr-2022

Accepted: 04-Apr-2022

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Funding: This research did not receive any financial support

Competing Interests: The authors have declared that no competing interests exist

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BACKGROUND: Shear wave elastography (SWE) represents a new, non-invasive method in reaching a final diagnosis of diffuse liver diseases. The method has been widely used instead of liver biopsy - an invasive procedure with rare, but potentially serious, complications. Compared to liver biopsy, SWE allows examination of larger liver areas, thus providing better staging of hepatic fibrosis.

AIM: The primary goal of our study was to determine the value of SWE and serum markers of fibrosis as diagnostic methods in the detection of liver fibrosis.

METHODS: A group of 30 patients were randomly included in the study on the basis of previous clinical, biochemical, and ultrasound findings indicating a presence of chronic liver lesion. Patients were divided into three groups: 6 patients with steatosis, 13 patients with viral hepatitis, and 11 patients with liver cirrhosis. Liver damage biochemical markers, serum markers indicating liver fibrosis, and SWE were determined in all patients.

RESULTS: Statistical analysis revealed a positive correlation between SWE results, and the values of biochemical markers of the hepatic lesion, as well as with the levels of serum liver fibrosis markers.

CONCLUSION: The analysis of the results has provided insight into the correlation between the values of SWE and the values of serum markers of liver fibrosis, and with the values of biochemical parameters of the hepatic lesion, i.e., patients with cirrhosis had an F4 value on elastography and higher values of serum fibrosis biomarkers according to biochemical markers for liver lesion, and in compliance with the results from the literature.

Introduction

Hepatic fibrosis is defined as the accumulation of connective tissue in the liver parenchyma, usually as a response to hepatocellular damage of various etiology: alcoholic, non-alcoholic/metabolic steatohepatitis, autoimmune and hereditary liver diseases, obstruction of hepatic veins, decompensated heart failure, or drug-induced liver injury.

In acute liver damage (e.g., caused by viral hepatitis), parenchymal cells regenerate and replace necrotic cells. When liver lesion persists, liver fibrosis occurs, with the final appearance of cirrhosis.

The accumulation of connective tissue in the liver parenchyma disrupts the specific lobular architecture leading to vascular insufficiency of hepatocytes and their dysfunction; as the lesion progresses, it may lead to liver cirrhosis and hepatic failure [1], [2].

It has been historically considered that fibrosis is irreversible and beyond the repair process, leading

to advanced liver disease, while the contemporary viewpoint is contrary: fibrosis is a reaction, i.e., a "response" to healing in cases of different types of chronic liver failure [3], [4], [5].

Liver fibrosis, which was practically ignored until the 1980s, has become the main topic by identifying stellate cells which are mesenchymal cells located in the space of Disse [6]. Stellate cells, described for the first time by Karl Wilhelm von Kupfer in 1876 who named them "Sternzellen" (hepatic stellate cells), are responsible for the formation of connective tissue in the liver [7]. The methods for extracting hepatic stellate cells from rodents and humans were standardized in the 1980s, and the culture of these cells was widely acknowledged as a model of study in their activated form. Experimental models for studying liver fibrogenesis in rodents were developed, confirming the research on cell culture and key fibrogenic mediators [7], [8], [9], [10], [11]. Except for hepatic stellate cells, it has been recently confirmed that portal myofibroblasts and the cells originating from bone marrow have the potential to create connective tissue [12], [13]. At the clinical level, liver fibrosis has been studied primarily in patients with hepatitis C viral

infection [14], [15]. In the 1990s, it was discovered that even advanced liver fibrosis is reversible, and researchers were stimulated to develop antifibrotic therapies which continue to be clinically tested [16], [17].

Hepatic fibrosis staging is an important indicator of both the path and the prognosis of the disease and is a key factor in determining the treatment options for these patients.

Even though liver biopsy is still a "gold standard" in the diagnosis of diffuse liver diseases, replacement of these invasive procedures with non-invasive procedures such as shear wave elastography (SWE) and serum markers of liver fibrosis are much more frequent in contemporary hepatology due to the minimum risk of complications and the possibility of examining a larger liver area, as well as foreseeing the evolution of the disease.

Aims

The primary goal of our study was to determine the value of SWE and serum markers of fibrosis as diagnostic methods in the detection of liver fibrosis.

Secondary goals

1. To determine the correlation between SWE and serum markers of fibrosis when diagnosing liver fibrosis
2. To determine the correlation between SWE and biochemical markers for hepatic lesion (liver enzymes, protein status, and coagulation status)
3. To determine the correlation between serum markers of liver fibrosis and biochemical markers of hepatic lesion.

Materials and Methods

Materials

The study is prospective and includes 30 patients randomly selected over a period of 2 years (2019 to 2021), and divided into three groups: patients with hepatitis, patients with steatosis (alcoholic and non-alcoholic), and patients with cirrhosis. The study was performed at the Clinic of Gastroenterohepatology and the Institute of Immunology and Human Genetics at the Faculty of Medicine in Skopje. The patient group is small due to the random selection of these patients with a specific diagnosis from a limited geographic distribution.

Inclusion criteria

Patients ranging in age from 18 to 80 years, who were diagnosed with liver lesions based on previous clinical and biochemical tests, and ultrasound examination, were included in the study.

Exclusion criteria

Patients with cardiopulmonary diseases, obese patients (body mass index over 30 kg/m²), patients with ascites, and patients with malignant disease were excluded from the study.

Methods

Biochemical markers for hepatic lesion: liver enzymes (alanine transaminase [ALT] and aspartate transaminase [AST]), platelet values, total bilirubin, prothrombin time and prothrombin index, SWE, and serum markers of liver fibrosis were tested in each patient.

Non-invasive methods for liver fibrosis staging

Shear wave elastography

Over the last decade, the expansion of science and technology has contributed to the development of many qualitative and quantitative methods of investigation, converting subjective "palpation" of the liver into an objective criterion.

Explaining SWE always starts with the simple example of a rock thrown into a lake, where we can see the wave diverging in a circular fashion toward the periphery. In the same way, the waves caused by the transducer of the ultrasound diverge through the tissue. The ultrasound registers the speed of wave propagation through the normal liver parenchyma and the reduced velocity when moving through fibrous tissue.

SWE is an imaging method for the indirect measurement of tissue elasticity. Each alteration of elasticity indicates morphologic alterations in the liver parenchyma.

This method was first introduced to our clinic in 2017, and it presents real-time sonography and shear wave measurement (SWM) simultaneously. Real-time elastography is a two-dimensional method that visualizes the elasticity of the tissue during the examination. SWM software, which is integrated into the Hitachi device, measures the speed of wave propagation through the tissue, thus determining liver elasticity. SWE is a non-invasive method and lasts approximately 15–30 min. The automatic result is the mean value calculated from 10 consecutive

measurements of the wave velocity moving through the tissue (shear wave velocity - Vs), with a quality index that expresses the percentage of efficient measurement (VsN - net amount of shear wave velocity), which cannot be less than 50%.

The result provides fibrosis staging, ranging from F0 to F4 (Figure 1), and is shown as one of the 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 the wave moving across the tissue.

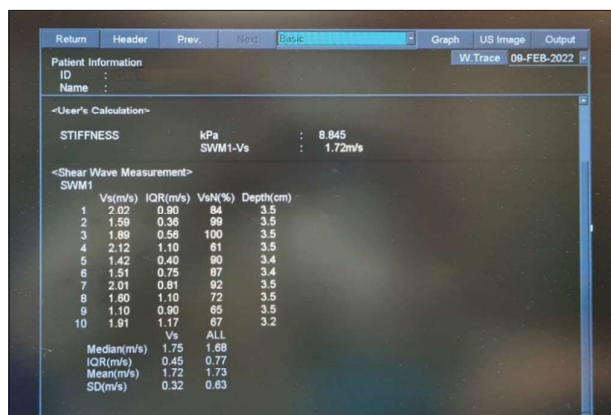


Figure 1: Calculating results when measuring liver fibrosis during shear wave elastography

When the value is 5.8 kPa or lower (4.4–5.5 kPa), there is no liver fibrosis (F0), and the liver is healthy. At F1, the value ranges between 5.9 and 7.2 kPa and indicates an initial stage of fibrosis. When the value is in the 7.3–9.5 kPa range, this indicates advanced fibrosis F2–F3, and when the value is above 9.6 kPa, this expresses F4 fibrosis which is equivalent to cirrhosis.

There are few technical limitations to this method: avoiding placing the region of interest on elastograms deep in the liver, over/close to blood vessels, in the liver angles, and less than 1.5 cm from the liver capsule (Figure 2).



Figure 2: Example of performing elastography in the right lobe of the liver. Example of correct placing of the region of interest during elastography

The limitations of this method are obese patients with tight intercostal spaces, the postprandial performance of the examination (abdominal gas), deep breathing during the examination, presence of ascites, extrahepatic cholestasis, or congestive heart failure.

In our study, real-time SWM was conducted using the ARIETTA V70 Hitachi Aloka device and convex C251 (1.8–5.0 MHz) transducer. The measurement was taken in accordance with the recommendations of the European Federation of Societies for Ultrasound in Medicine and Biology [18].

Serum markers of liver fibrosis

Serum markers are fragments of the extracellular matrix (ECM) components, produced by liver stellate cells during the process of fibrinogenase and fibrinolysis, which are divided into direct and indirect markers of liver fibrosis. Direct markers of liver fibrosis are produced by stellate and other cells during the production and decomposition of the ECM in the case of liver lesions. Serum levels of these markers increase as the fibrosis progresses, and they tend to reduce in response to different treatments [19].

According to their molecular structure direct markers can be classified as follow: collagens (procollagen type I carboxy terminal peptide (PICP), procollagen type III amino terminal peptide (PIIINP), collagen type I and collagen type IV), glycoproteins and polysaccharides (hyaluronic acid, laminin and human cartilage glucoprotein (YKL-40)), collagenases and their inhibitors (matrix metalloproteinase (MMP) and tissue inhibitors of MMP (TIMIs)), and cytokines and proteomic markers [20], [21], [22], [23], [24], [25].

Direct markers according to the stellate cell production can be classified in: direct markers that appears during the period of production of ECM (procollagen type I carboxy terminal peptide (PICP), procollagen type III amino terminal peptide (PIIINP), collagen type I, collagen type IV and laminin) and direct markers that appears during the period of decomposition of ECM (matrix metalloproteinase (MMP) and tissue inhibitors of MMP (TIMIs)).

Indirect markers of liver fibrosis are aminotransferases, alkaline phosphatase, γ -glutamyl transferase, bilirubin, albumin, prothrombin time and AAP index (AST/ALT), APRI score (AST/Tr ratio), as well as other indices: Forns, FibroTest, FibroSure test, Fibro index, a result of Fibrosis-4 index (FIB-4), FibroQ test, SteatoTest, and many others [26].

By applying the method of chemiluminescence, the Institute of Immunology and Human Genetics tested 30 patients for the concentration of direct serologic markers of liver fibrosis such as procollagen type III

amino-terminal peptide (PIIINP), collagen IV, and hyaluronic acid.

Statistical analysis

The statistical processing and analysis of the data were carried out using the IBM SPSS Statistics 23 software for Windows. The Shapiro–Wilk test was used for testing normalcy in the data distribution.

Quantitative markers were displayed with arithmetic mean, standard deviation, minimum and maximum values, median, and interquartile ranges, while qualitative markers were displayed with absolute and relative numbers.

Chi-square test, analysis of variance, and the Kruskal–Wallis test were used for comparing the groups with hepatitis, steatosis, and cirrhosis.

Non-parametric correlation (Spearman's rank coefficient of correlation) was used for determining the relationship between the stage of liver fibrosis with serum and biochemical markers of fibrosis.

The value $p < 0.05$ was considered statistically significant.

The collected data are displayed in tables.

Results

The study comprises 30 patients, divided into three groups: 13 patients with viral hepatitis, 6 patients with alcoholic and non-alcoholic steatosis, and 11 patients with liver cirrhosis.

The mean age and gender distribution of patients are displayed in Table 1. Patients with viral hepatitis, steatosis, and cirrhosis had an average age of 50.9 ± 16.2 , 57.0 ± 14.9 , and 59.0 ± 10.7 years. In the female group, the most frequent diagnosis was liver cirrhosis - 54.55% (6 patients), while in the male group, the most frequent diagnosis was viral hepatitis - 53.85% (7 patients). The difference between the three groups according to the average age and gender distribution ($p > 0.05$) was statistically insignificant, i.e., the three groups were homogeneous regarding the age and gender structure.

Table 1: Mean age and gender distribution of patients with hepatitis, steatosis, and cirrhosis

Age Distribution				
Group	Descriptive statistics			p-level
	n	Mean $\pm$ SD	Minimum–maximum	
Hepatitis	13	50.9 $\pm$ 16.2	29–72	F = 1.0, P = 0.37 (NS)
Steatosis	6	57.0 $\pm$ 14.9	41–75	
Cirrhosis	11	59.0 $\pm$ 10.7	45–76	
Gender Distribution				
Group	Descriptive statistics			p-level
	n	Female, n (%)	Male, n (%)	
Hepatitis	13	6 (46.15)	7 (53.85)	χ^2 = 0.17, P = 0.92 (NS)
Steatosis	6	3 (50.0)	3 (50.0)	
Cirrhosis	11	6 (54.55)	5 (45.45)	

F: Analysis of variance, χ^2 : Chi-square test, SD: Standard deviation, NS: Not significant.

This study analyzes the relationship between biochemical hepatic markers (AST, ALT, platelets, bilirubin, prothrombin time, and INR index) and the stage of fibrosis.

Patients with hepatitis, steatosis, and cirrhosis had no significant differences concerning serum values of ALT ($p = 0.69$), prothrombin time ($p = 0.22$), and INR ($p = 0.21$).

Serum values of AST, platelets, and serum bilirubin were significantly different depending on the stage of fibrosis (total significant differences of $p = 0.0039$, $p = 0.028$, and $p = 0.019$, respectively, for AST, platelets, and bilirubin).

Patients with cirrhosis had significantly higher AST values compared to patients with steatosis (median: 45 vs. 18.5; $p = 0.0027$) and significantly lower platelets compared to patients with steatosis (mean: 139.96 ± 87.6 vs. 236.83 ± 46.8 ; $p = 0.023$). Serum bilirubin had significantly higher values in patients with cirrhosis compared to patients with hepatitis (median: 21 vs. 9.5; $p = 0.019$) (Table 2).

Comparative results of serum markers of fibrosis procollagen type 3 PIIINP and collagen type 4 had insignificantly different values depending on the stage of fibrosis ($p = 0.45$ and $p = 0.56$, respectively), while the values of hyaluronic acid differed significantly in patients with hepatitis, steatosis, and cirrhosis ($p = 0.038$). The *post hoc* analysis demonstrated that this significant difference is due to the significantly higher values of hyaluronic acid in the group of patients with cirrhosis compared to the group of patients with hepatitis (median: 121.6 vs. 53.99; $p = 0.039$) and with the group of patients with steatosis (median: 121.6 vs. 50.73; $p = 0.046$) (Table 3).

Mean values of shear wave liver elastography were highest in the group with cirrhosis (16.07 ± 4.9), followed by the group with hepatitis and steatosis (7.36 ± 1.9 vs. 6.52 ± 1.7 , respectively). According to the results of the statistical analysis, the values differed significantly depending on the stage of fibrosis ($p = 0.000001$). *Post hoc* analysis showed that this total significant difference is due to the significantly higher mean values in patients with cirrhosis compared to the patients with hepatitis ($p = 0.00013$), and to the significantly higher average values in patients with cirrhosis compared to patients with steatosis ($p = 0.00014$) (Tables 4 and 5).

The tested correlations between the value of SWE and the analyzed hepatic biochemical and serum markers of fibrosis have indicated that SWE significantly correlates with AST ($p = 0.0016$), bilirubin ($p = 0.014$), INR ($p = 0.03$), and hyaluronic acid ($p = 0.044$) (Table 6). According to the value in the Spearman's rank correlation coefficient, all of these significant correlations are positive, i.e., direct ($R=0.552$, $R=0.442$, $R=0.395$, and $R=0.37$, respectively, for the correlation with ACT, bilirubin, INR, and hyaluronic acid), which indicates that the value of SWE is increased by increasing these markers, and vice versa.

Procollagen type III amino terminal peptide (PIIINP) has a significant positive correlation with AST ($R = 0.484$, $p = 0.007$), with INR ($R = 0.396$, $p = 0.03$), and with prothrombin time ($R = 0.494$, $p = 0.0055$). In patients with hepatic fibrosis, procollagen type III amino terminal peptide (PIIINP) was increased by increasing serum values of AST, INR, and with prothrombin time, and vice versa.

Collagen 4 marker has a positive significant correlation with the marker INR ($R = 0.465$, $p = 0.0096$), i.e., its value increases by increasing the procollagen type 3 PIIINP, and vice versa.

Hyaluronic acid was increased by reducing the number of platelets, and vice versa. This statistical comment is a result of a confirmed significant negative correlation between the hyaluronic acid and the number of platelets ($R = -0.467$, $p = 0.011$).

Discussion

In daily clinical practice, we face diffuse liver diseases of different etiology and stages, ranging from chronic viral or toxic hepatitis, fatty liver (from alcoholic and non-alcoholic etiology), autoimmune and metabolic liver diseases, to liver cirrhosis as a final stage of chronic liver disease.

Table 2: Correlation between biochemical hepatic markers and the stage of fibrosis

Group	Statistical parameter				p-level
	n	Mean $\pm$ SD	Minimum–maximum	Median (IQR)	
ACT					
Hepatitis	13	88.48 $\pm$ 188.5	19–711	26.3 (23–40)	H = 11.1, P = 0.0039** significant 2 versus 3 P = 0.0027**
Steatosis	6	18.67 $\pm$ 7.8	6–27	18.5 (16–26)	
Cirrhosis	11	76.64 $\pm$ 79.1	23–299	45 (29–84)	
ALT					
Hepatitis	13	78.32 $\pm$ 124.9	14–473	31.18 (21–67)	H = 0.73, P = 0.69 (NS)
Steatosis	6	33.67 $\pm$ 18.9	11–57	33.5 (18–49)	
Cirrhosis	11	52.64 $\pm$ 42.8	13–159	37 (24–71)	
Platelets					
Hepatitis	13	186.54 $\pm$ 54.7	80–269		F = 4.098, P = 0.028* significant 2 versus 3, P = 0.023* significant
Steatosis	6	236.83 $\pm$ 46.8	176–318		
Cirrhosis	11	139.96 $\pm$ 87.66	1.6–316		
Bilirubin					
Hepatitis	13	12.01 $\pm$ 9.4	4.42–41	9.5 (6.8–12.5)	H = 8.6, P = 0.019* significant 1 versus 3 P = 0.019* significant
Steatosis	6	10.80 $\pm$ 4.3	6.2–18.4	10.5 (7.4–11.8)	
Cirrhosis	11	34.62 $\pm$ 33.1	6.1–124.8	21 (19.2–41)	
Prothrombin time					
Hepatitis	13	12.28 $\pm$ 1.6	10.4–16		F = 1.59, P = 0.22 (NS)
Steatosis	6	11.95 $\pm$ 0.8	11.1–13.4		
Cirrhosis	11	13.51 $\pm$ 2.7	11.7–21.3		
INR					
Hepatitis	13	1.07 $\pm$ 0.2	0.91–1.49	1 (0.99–1.08)	H = 3.14, P = 0.21 (NS)
Steatosis	6	1.06 $\pm$ 0.1	0.98–1.21	1.03 (1–1.09)	
Cirrhosis	11	1.17 $\pm$ 0.3	0.99–2.06	1.09 (1.02–1.12)	

* $p < 0.05$, ** $p < 0.01$, F: Analysis of variance, *post hoc* Tukey's test, H: Kruskal–Wallis test, Mann–Whitney *post hoc*, SD: Standard deviation, NS: not significant, IQR: Interquartile range, p-value: probability value, AST: aspartate aminotransferase, ALT: alanine aminotransferase, INR: international normalized ratio.

Liver cirrhosis and its complications, such as portal hypertension and hepatocellular failure, represent a significant problem for the patient as well as for the whole healthcare system, due to an increasing number of hospitalizations, bad quality of life, and heavy financial burden. As mentioned above, liver fibrosis occurs and progresses in cirrhosis when liver lesion persists.

Table 3: Correlation of serum markers with the stage of fibrosis

Group	Statistical parameter				p-level
	n	Mean $\pm$ SD	Minimum–maximum	Median (IQR)	
Procollagen type 3 amino-terminal peptide					
Hepatitis	13	26.99 $\pm$ 15.2	8–54.54	22.48 (15.76–32.84)	H = 1.59, P = 0.45
Steatosis	6	20.40 $\pm$ 2.7	16.3–24.28	20.76 (18.77–21.52)	(NS)
Cirrhosis	11	38.22 $\pm$ 27.1	11.71–99.03	30.67 (15.76–48.17)	
Collagen type 4					
Hepatitis	13	24.61 $\pm$ 15.9	10–61.91	18.6 (13.42–30.48)	H = 1.016, P = 0.56
Steatosis	6	43.02 $\pm$ 58.6	14.58–162.4	19.24 (17.75–24.88)	(NS)
Cirrhosis	11	32.97 $\pm$ 24.0	2–91.21	30.8 (13.42–46.49)	
Hyaluronic acid					
Hepatitis	13	74.33 $\pm$ 47.6	11.82–161.1	53.99 (31.7–116.3)	H = 6.52, P = 0.038*
Steatosis	6	59.61 $\pm$ 43.9	17.34–141.5	50.73 (31.98–65.34)	significant 1 versus 3
Cirrhosis	11	146.92 $\pm$ 94.3	31.7–318.3	121.6 (74.49–213.8)	P = 0.039* significant 2 versus 3 P = 0.046* significant

* $p < 0.05$, H: Kruskal–Wallis test, NS: Not significant, SD: Standard deviation, IQR: Interquartile range.

The hepatic biopsy is still the gold standard in staging liver cirrhosis both in our country and worldwide. The method is invasive, unpleasant for the patient, and may be followed by rare complications.

Table 4: Descriptive statistic analysis of SWE in patients with hepatitis, steatosis and cirrhosis

Group	Descriptive statistics (SWE/kPa)			p-level
	n	Mean $\pm$ SD	Minimum–maximum	
Hepatitis	13	7.36 $\pm$ 1.9	4.76–11.95	F = 25.34, P = 0.00001*** significant 1 versus 3 P = 0.00013*** significant 2 versus 3 P = 0.00014*** significant
Steatosis	6	6.52 $\pm$ 1.7	5.2–9.48	
Cirrhosis	11	16.07 $\pm$ 4.9	9.81–25.2	

*** $p < 0.0001$. F: Analysis of variance; *post hoc* Tukey's test, SWE: Shear wave elastography, SD: Standard deviation.

Pain is a common but mild complication in 84% of patients undergoing biopsy but often disappears after receiving small doses of narcotics immediately after biopsy [27]. 0.5% of patients have severe and lasting pain, particularly in cases of active bleeding or organ damage near the liver during the biopsy [28].

Table 5: Correlation of shear wave elastography with the stage of fibrosis

SWE (kPa)	n	Groups		
		Hepatitis, n (%)	Steatosis, n (%)	Cirrhosis, n (%)
F0				
F1	2	1 (7.69)	1 (16.67)	0
F2	6	5 (38.46)	1 (16.67)	0
F3	2	0	1 (16.67)	1 (9.09)
F4	9	0	0	9 (81.82)
F1–F2	4	4 (30.77)	0	0
F3–F4	2	1 (7.69)	0	1 (9.09)
F0–F1	5	2 (15.38)	3 (50)	0

SWE: Shear wave elastography, F0–F1 (no fibrosis), F0 (healthy liver), F1 (initial degree of fibrosis), F2 (advanced fibrosis), F3 (expressed fibrosis), F4 (cirrhosis).

Table 6: Correlations between the value of shear wave elastography and hepatic biochemical and serum markers for fibrosis, as well as the correlations of biochemical markers with serum markers of liver fibrosis

Biochemical and serum markers for liver fibrosis	Shear wave		Procollagen type 3 amino-terminal peptide		Collagen 4		Hyaluronic acid	
	Spearman R	p-level	Spearman R	p-level	Spearman R	p-level	Spearman R	p-level
AST	0.552	0.0016**	0.484	0.007**	0.175	0.35	0.11	0.57
ALT	0.062	0.74	0.292	0.117	-0.055	0.77	-0.042	0.82
Platelets	0.229	0.22	0.049	0.78	-0.017	0.93	-0.467	0.011*
Bilirubin	0.442	0.014*	0.098	0.6	-0.036	0.85	0.232	0.22
INR	0.395	0.03*	0.396	0.03*	0.465	0.0096**	0.088	0.64
Prothrombin time	0.312	0.09	0.494	0.0055**	0.325	0.08	0.142	0.45
Procollagen type 3 amino terminal peptide	0.31	0.094						
Collagen 4	0.314	0.091						
Hyaluronic acid	0.37	0.044*						

*p < 0.05, **p < 0.0001, p-value: probability value, AST: aspartate aminotransferase, ALT: alanine aminotransferase, INR: international normalized ratio.

[29], [30]. Infrequently, and at a lower percentage, severe complications may occur (internal bleeding, pneumothorax, and perforation of the large intestine and gallbladder).

The discovery of non-invasive methods to diagnose and stage liver fibrosis has contributed to the advance of contemporary hepatology which avoids invasive diagnostic procedures.

In our country, traditional non-invasive methods which are used in daily practice for examining the liver, such as abdominal ultrasound, computed tomography as well as biochemical markers for hepatic lesion have been, and still are, basic parameters used for the diagnosis and further treatment of liver diseases. These play a major role in detecting organ damage but not in predicting and diagnosing early stages of hepatic fibrosis.

Recently, several non-invasive methods have been developed to measure liver elasticity, thus staging its lesions, such as transitory elastography, SWE, and strain elastography. Over the last decade, we have used more non-invasive methods in staging liver fibrosis, i.e., serum markers for liver fibrosis are tested and SWE is performed, which also represents a real-time elastography and SWM. The method is two-dimensional.

Several studies have been conducted worldwide on patients with normal and hepatic lesions, using invasive and non-invasive methods, comparing and demonstrating that there is a positive correlation between these in staging hepatic fibrosis.

There have been a small number of studies conducted worldwide that compare the results of elastography with biochemical markers of the hepatic lesion and with serum markers of liver fibrosis. These are contradictory and refer more to transitory elastography.

This study has several limitations. Half of our patients did not undergo a liver biopsy, which is the main standard serving as a basis for staging liver fibrosis. The limitation refers to the small group

of patients and there are not sufficient studies comparing the three parameters of non-invasive methods for staging liver fibrosis, thus making the comparison with other studies around the world more difficult.

Conclusion

Our study analyzed the correlation between biochemical liver parameters (AST, ALT, platelets, bilirubin, prothrombin time, and INR index) with the fibrosis stage. Patients with cirrhosis had significantly higher AST values compared to patients with steatosis and significantly lower platelets compared to patients with steatosis. Compared to patients with hepatitis, there were significantly higher values of serum bilirubin in patients with cirrhosis.

Comparative results of serum markers of fibrosis procollagen type 3 PIIINP and collagen type 4 showed insignificantly different values depending on the stage of fibrosis, while the values of hyaluronic acid were significantly higher in the group of patients with cirrhosis compared to the group of patients with hepatitis and with the group of patients with steatosis.

Mean values of SWE were highest in the group with cirrhosis, followed by the group with hepatitis and then steatosis.

The examined correlations between the value of SWE and the analyzed hepatic biochemical and serum markers for fibrosis have indicated that SWE had a significant positive correlation with AST, bilirubin, INR, and hyaluronic acid. Procollagen type 3 PIIINP had a significant positive correlation with AST, with INR, and with prothrombin time. Collagen 4 marker had a significant positive correlation with the INR marker. There was a confirmed significant negative correlation between hyaluronic acid and the number of platelets.

The analysis of the results has provided insight into the correlation between the values of SWE and the values of serum markers of liver fibrosis, and with the values of biochemical parameters of the hepatic lesion, i.e., patients with cirrhosis had an F4 value on elastography and higher values of serum fibrosis biomarkers according to biochemical markers for liver lesion, and in compliance with the results from the literature.

We hope that in future, we can confirm the validity of our results with a study encompassing a larger number of patients with different types of diffuse liver diseases.

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