

## Real Time Elastography Assessment of Fibrosis In Chronic Viral Hepatitis

C.F. JIEANU<sup>1</sup>, B.S. UNGUREANU<sup>1</sup>, DANIELA LARISA SANDULESCU<sup>1</sup>,  
D.O. ALEXANDRU<sup>2</sup>, G.S. FIRU<sup>1</sup>, D.I. GHEONEA<sup>1</sup>, I.ROGOVEANU<sup>1</sup>,  
S. CAZACU<sup>1</sup>, T. CIUREA<sup>1</sup>, A. SAFTOIU<sup>3</sup>

<sup>1</sup>First Clinic of Internal Medicine, Department of Gastroenterology, Clinical County Emergency Hospital of Craiova

<sup>2</sup>Department of Medical Informatics and Biostatistics, University of Medicine and Pharmacy of Craiova

<sup>3</sup>Department of Endoscopy, Gastrointestinal Unit, Copenhagen University Herlev Hospital

**ABSTRACT:** Fibrosis assessment is a necessary component of liver disease evaluation not only for prognosis but also for future therapeutic management. **Our study objective** was to evaluate the accuracy of quantitative assessment of liver fibrosis in patients with chronic viral hepatitis B or C, relying on RTSE results, a method approved and acknowledged in Europe. **Material and Methods.** Sixty-three consecutive patients diagnosed with chronic viral hepatitis B or C between January 2014 and December 2014 at the Emergency County Hospital of Craiova were enrolled in the study. Patients underwent both TE and RTSE. **Results.** The reference method used for staging liver fibrosis was TE, based on its recognition and validation by the European guidelines. Fibrosis was classified as follows: 17.47% of patients were staged as F0, 11.11% of patients staged as F1, 14.28% as F2, 17.47% as F3, and 39.68% as F4. Correlation coefficients between measurements for each parameter was done with ANOVA test, in order to identify any differences, according to the fibrosis stage. Valuable information was obtained suggesting that MEAN, SD, %AREA, COMP, Skewness, IDM and Contrast had highly significant differences when related to the Fibrosis Stage (FS) ( $p < 0.001$ ) and ASM had significant differences ( $p < 0.05$ ). As for Kurtosis, ENT and Correlation parameters no significant differences with the FS was found. **Conclusions.** Imaging methods of assessing liver fibrosis are of special interest in chronic liver fibrosis assessment. RTSE comes as a potential new technology based on elastogram evaluation which may prove to be more efficient along with larger prospective studies.

**KEYWORDS:** TE, RTSE, Fibrosis stage, chronic viral hepatitis

### Introduction

Progress staging of liver fibrosis in chronic viral hepatitis is considered an important factor of liver disease with a certain evolution to cirrhosis or hepatocellular carcinoma. Hence, fibrosis assessment is a necessary component of liver disease evaluation not only for prognosis but also for future therapeutic management[1].

Traditionally, the golden standard for fibrosis quantification is considered the histopathological diagnosis. However, due its invasiveness, with potential bleeding, different histopathological interpretation or sampling error, the current tendency leans over non-invasive imagistic methods. [2,3,4,5,] Recent developments have certified that liver stiffness might also be evaluated by other techniques such as serological testing or specific imaging methods: ultrasound (US) or magnetic resonance imaging (MRI). [6,7]

Transient Elastography (TE/Fibroscan) is the first non-invasive US-based method for liver stiffness assessment approved and certified for hepatitis B and C, by the European guidelines and by national and international US societies. [1,8] So far, many reports have confirmed Fibroscan as a reliable and representative way of

assessing fibrosis, which is why we used TE as the baseline method of our study.

Another way of measuring tissue elasticity in chronic viral hepatitis might be done with Real-Time Elastography (RTSE), a rather novel method when it comes to liver fibrosis assessment. Using a modified-US equipment the echo signals are captured in real time while the degree of distortion obtained after compression is translated in color-coded images. Due to its characteristics RTSE may even surpass the flaws of Fibroscan when encountering narrow intercostal spaces, ascites or obese patients. [9,10,11]RTSE has proven its efficacy in patients with chronic hepatitis C, however a relatively few studies have been published so far on hepatic fibrosis evaluation in HBV infection. [12]

Our study objective was to evaluate the accuracy of quantitative assessment of liver fibrosis in patients with chronic viral hepatitis B or C, relying on RTSE results, a method approved and acknowledged in Europe.

### Materials and Methods

#### Patients

Sixty-three consecutive patients diagnosed with chronic viral hepatitis B or C between

January 2014 and December 2014 at the Emergency County Hospital of Craiova were enrolled in the study. Viral hepatitis diagnosis was defined by the presence of serum anti HCV antibody or serum hepatitis B surface antibody for more than 6 months. Exclusion criteria included patients with hepatitis of other etiology than viral infection, fatty liver disease, patients with history of drugs or alcohol abuse as well as cardiopulmonary disorders.

This prospective study was performed after an informed consent was signed by each enrolled patient, according to the Declaration of Helsinki. Also it was approved by the local ethics committee (No 110/2014). Both imaging methods TE and RTSE were evaluated in the same day by different clinicians, with patients under fasting conditions.

### Transient Elastography

Transient elastography was performed using a FibroScan® device (EchoSens, Paris, France) with the patient lying in dorsal decubitus position, with the right arm in abduction. Two types of transducers were used, the M and XL probes which generated a measured pressure between 2.5 to 75 kPa. The tip of the transducers was placed over an interspace of the ribcage of the right upper quadrant, corresponding to the right liver lobe. The mean of ten measurements was considered the final result of fibrosis evaluation, with all the acquisitions that did not receive a correct vibration being rejected. Only patients who had a success rate > 60%, with an interquartile range (IQR) < 30% were included in this study.

### Real Time Elastography

Real Time Ultrasound Elastography was carried out with a 7-3 MHz (EUP-L52) linear transducer from Hitachi Preirus equipment (Hitachi Aloka Medical Tokyo, Japan). Initially, using a convex transducer a standard ultrasound examination was performed. Following the heart direction, the US probe was positioned within the V-VIII intercostal spaces, between the anterior and middle axillary line, targeting the right liver lobe.

The elastic strain induced by liver tissue was dependant on the heartbeat [14]. The interest region (ROI) was set inside the liver parenchyma, 1 cm under the liver capsule, in a selected box of 1/2.5 cm. The area of interest was chosen so that the 2D image was as clear as possible, the large vessels and the artifacts given by ribs and lungs avoided. For each patient we recorded 3 different clips, that included a stable

elastography image of at least 5 heart beats. A sequence on the negative pick was selected, and a value for each film was calculated. Everything was saved in the report and in data base, along with the 11 parameters given by the using the software Elasto\_ver 1.5.1, kindly provided by Hitachi, such as: mean relative strain value (MEAN); standard deviation of relative strain value (SD); percentage of low strain area (percentage of blue color area – %AREA); complexity of low strain area (calculated as perimeter<sup>2</sup>/area – COMP); skewness (SKEW); kurtosis (KURT); contrast (CONT); entropy (ENT); textural complexity, inverse difference moment (IDM); angular second moment (ASM); Correlation (CORR) indicates the feature value of the texture directivity. Liver fibrosis index (LFI) was also given by the Strain Histogram measurement software.

LFI was calculated as follows:

$$-0.009 \times \text{MEAN} - 0.005 \times \text{SD} + 0.023 \times \% \text{AREA} + 0.025 \times \text{COMP} + 0.775 \times \text{SKEW} - 0.281 \times \text{KURT} + 2.083 \times \text{ENT} + 3.042 \times \text{IDM} + 39.979 \times \text{ASM} - 5.542 \quad [15, 16]$$

For each patient included in the study, we recorded the mean of two parameters: LFI and MEAN - mean of the relative strain value within the ROI.

### Statistical Analysis

Statistical analysis was performed using Microsoft Excel (Microsoft Corp., Redmond, WA, USA), together with the XLSTAT add-on for MS Excel (Addinsoft SARL, Paris, France) and IBM SPSS Statistics 20.0 (IBM Corporation, Armonk, NY, USA) for processing the data.

To test the normality of the data we used the Anderson-Darling test. Because the numerical variables investigated had a normal distribution of data, globally or inside each studied group, we were allowed to use parametric statistical tests (e.g. ANOVA test followed by post-hoc analysis with Fisher's LSD test, Pearson Correlation coefficient) and the results summarized as mean value ± standard deviation.

### Results

This study included 63 patients, of which 19 were diagnosed with HBV infection, while 44 had chronic hepatitis C. The reference method used for staging liver fibrosis was TE, based on its recognition and validation by the European guidelines. We used the latest published cut-offs proposed in the Tsochatzis meta-analysis [17]. For patients with chronic viral hepatitis C, cut-

off values for F2, F3 and F4 were 7,6 kPa, 10,9 kPa and 15,3 kPa, respectively. For hepatitis B group cut-off values used were 7 kPa, 8,2 kPa and 11,3 kPa.

Fibrosis was classified as follows: 11 patients (17.47%) were staged as F0, 7 patients staged as F1 (11.11), 9 patients as F2 (14.28%), 11 as F3 (17.47%), and 25 as F4 (39.68%).

#### RTSE Fibrosis Assessment

Analysis of the measurements for each parameter was done with ANOVA test, in order

to identify any differences, according to the fibrosis stage (FS). Valuable information was obtained suggesting that MEAN, SD, %AREA, COMP, Skewness, IDM and Contrast had highly significant differences when related to the Fibrosis Stage ( $p < 0,001$ ) and ASM had significant differences ( $p < 0,05$ ). As for Kurtosis, ENT and Correlation parameters no significant differences with the Fibrosis Stage was found ( $p > 0,05$ ).

**Table 1. Comparison of the analysed parameters, according to fibrosis stage (FS)**

Parameter	F0	F1	F2	F3	F4	Total	p ANOVA	Significance
MEAN	115.38 ± 5.46	112.02 ± 8.35	101.14 ± 12.25	88.37 ± 18.88	84.41 ± 15.10	96.58 ± 18.49	< 0.0001	HS
SD	49.86 ± 12.26	54.64 ± 9.67	70.66 ± 4.30	62.83 ± 9.77	67.59 ± 6.59	62.20 ± 11.22	< 0.0001	HS
%AREA	15.02 ± 7.82	19.56 ± 7.75	33.75 ± 8.93	39.34 ± 15.85	44.18 ± 10.69	33.40 ± 15.77	< 0.0001	HS
COMP	21.80 ± 4.56	22.70 ± 5.67	31.88 ± 5.70	38.52 ± 18.02	40.94 ± 12.18	33.42 ± 13.64	< 0.0001	HS
KURT	2.61 ± 0.27	2.51 ± 0.24	2.24 ± 0.15	2.71 ± 0.64	2.65 ± 0.59	2.58 ± 0.49	0.251	NS
SKEW	0.22 ± 0.10	0.26 ± 0.11	0.40 ± 0.18	0.59 ± 0.36	0.68 ± 0.27	0.49 ± 0.30	< 0.0001	HS
ENT	3.81 ± 0.07	3.82 ± 0.11	3.77 ± 0.11	3.66 ± 0.20	3.90 ± 1.24	3.81 ± 0.77	0.946	NS
IDM	0.11 ± 0.01	0.11 ± 0.01	0.14 ± 0.03	0.16 ± 0.05	0.18 ± 0.07	0.15 ± 0.06	0.0005	HS
ASM	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.02	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.01	0.005	S
CONT	175.96 ± 77.01	196.94 ± 64.36	296.41 ± 23.45	262.57 ± 64.19	289.72 ± 48.96	252.71 ± 73.47	< 0.0001	HS
CORR	0.97 ± 0.00	0.97 ± 0.00	0.97 ± 0.00	0.97 ± 0.01	0.97 ± 0.01	0.97 ± 0.01	0.602	NS

The ANOVA test was performed to check for differences between the elastographic parameters. MEAN, SD, % AREA, COMP, Skewness, IDM and Contrast have high significant differences regarding FS ( $p < 0,001$ ), ASM has significant differences ( $p > 0,05$ ), while Kurtosis, ENT and Correlation do not have significant differences ( $p > 0,05$ ).

The post-hoc analysis with Fisher's LSD revealed that in the MEAN parameter, F3 and F4 values are both smaller than F0, F1 and F2, and that F2 values are smaller than F0. Concerning SD, F2, F3 and F4 values are greater than F0 and F1, with statistical significance. Analysing percentage of area (%AREA) values, using Fisher's LSD test, we proved that F0 and F1 values are significantly lower than values for F2, F3 and F4, and also that values for F2 are lower

than values for F4. For COMP values, we showed that values for F0 and F1 are significantly lower than values for F3 and F4. As stated in the beginning, there were no statistically significant differences for Kurtosis and ENT values. Analysing the data for Skewness, we found that F3 and F4 values are both greater than F0, F1, and that F2 values are also smaller than F4 values. Analysing the data for IDM, we found that F3 and F4 values are both greater than F0, F1, and that F2 values are also smaller than F4 values. For ASM we could only show statistically significant differences between F4 and F0, or F1. Contrast values had significant differences between F0 and F1 versus, F2, F3 and F4, with lower grades having lower contrast values. There were no significant differences for Correlation values among

different fibrosis stages. Analysis of all 11 parameters showed that the fibrosis stage is inversely related with the MEAN value and directly proportional with SD, %AREA, COMP, Skewness, IDM, ASM and Contrast, all the correlation being highly statistically significant.

Further analysing the data for MEAN, we found that F3 and F4 values are both smaller than F0, F1 and F2, and that F2 values are smaller than F0.

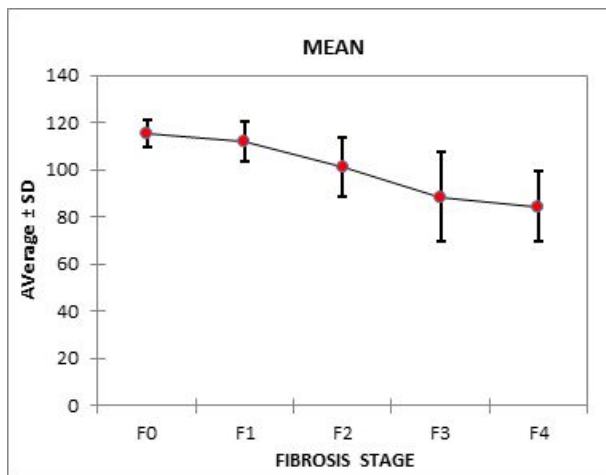


Fig.1. Comparison of MEAN according to FS

Concerning SD, we found, from the ANOVA post-hoc analysis, using Fisher's LSD test, that values for F2, F3 and F4 are greater than values for F0 and F1, with statistical significance

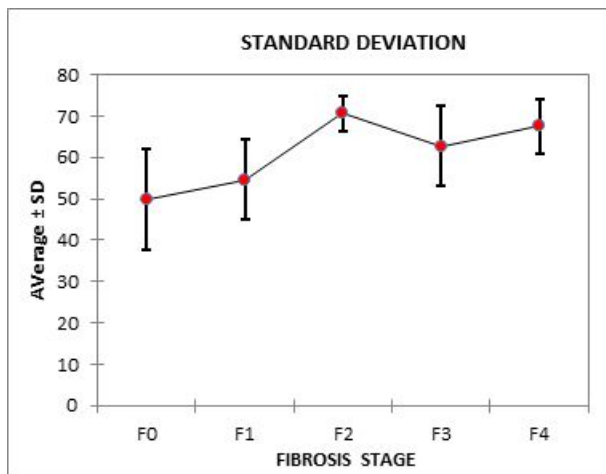


Fig.2. Comparison of STANDARD DEVIATION according to FS

Analysing percentage of area (%AREA) values, using Fisher's LSD test, we proved that F0 and F1 values are significantly lower than values for F2, F3 and F4, and also that values for F2 are lower than values for F4.

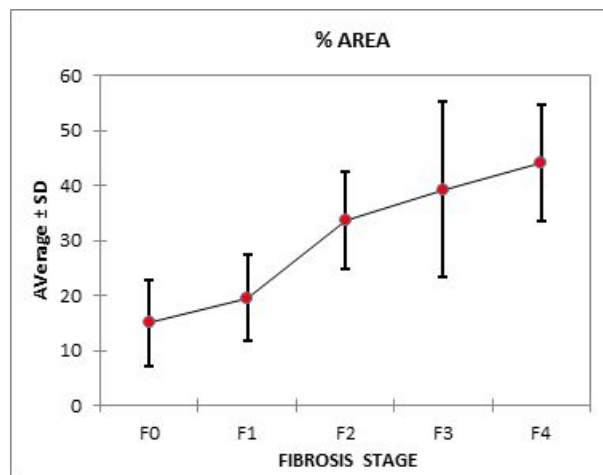


Fig.3. Comparison of %AREA according to FS

For COMP values, we showed that values for F0 and F1 are significantly lower than values for F3 and F4.

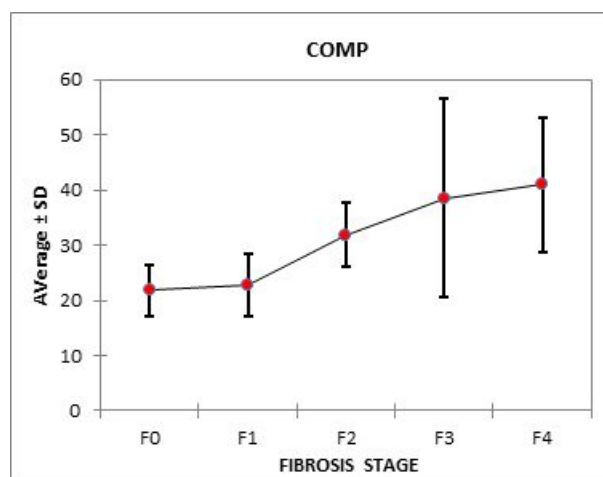


Fig.4. Comparison of COMP according to FS

As stated in the beginning, there were no statistically significant differences for Kurtosis values.

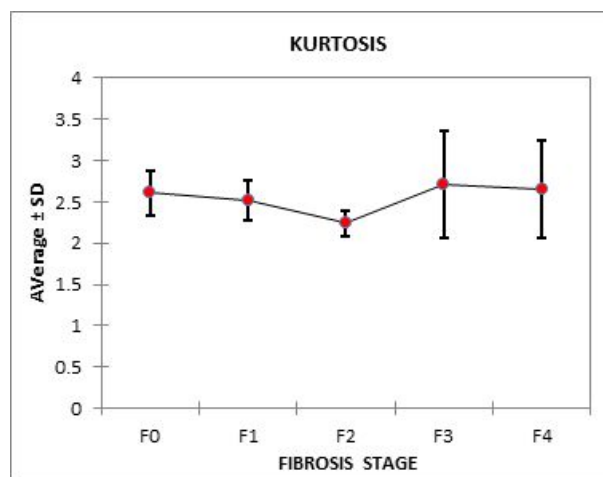


Fig.5. Comparison of KURTOSIS according to FS

Analysing the data for Skewness, we found that F3 and F4 values are both greater than F0, F1, and that F2 values are also smaller than F4 values.

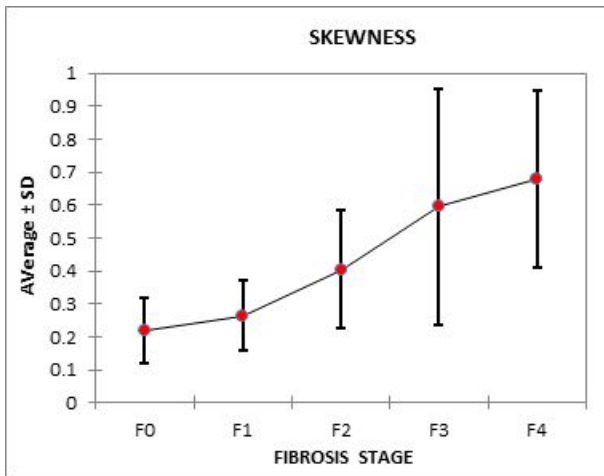


Fig.6. Comparison of SKEWNESS according to FS

As stated in the beginning, there were no statistically significant differences for ENT values.

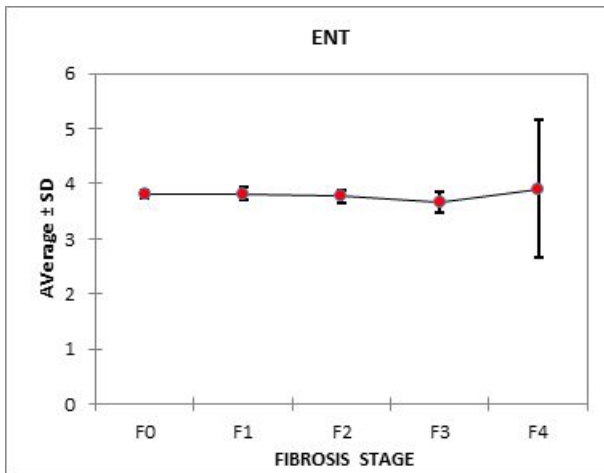


Fig.7. Comparison of ENT according to FS

Analysing the data for IDM, we found that F3 and F4 values are both greater than F0, F1, and that F2 values are also smaller than F4 values.

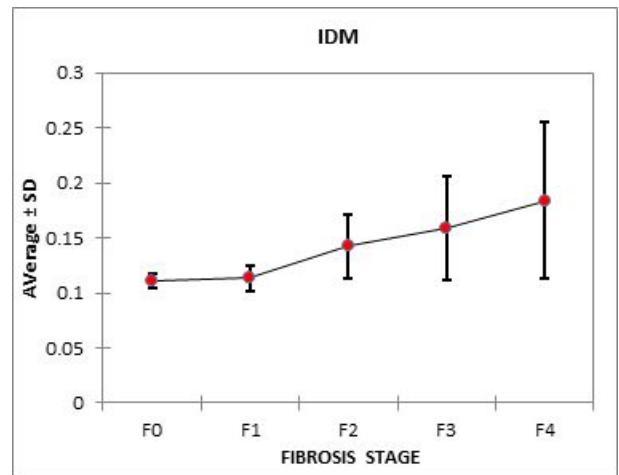


Fig.8. Comparison of IDM according to FS

For ASM we could only show statistically significant differences between F4 and F0, or F1.

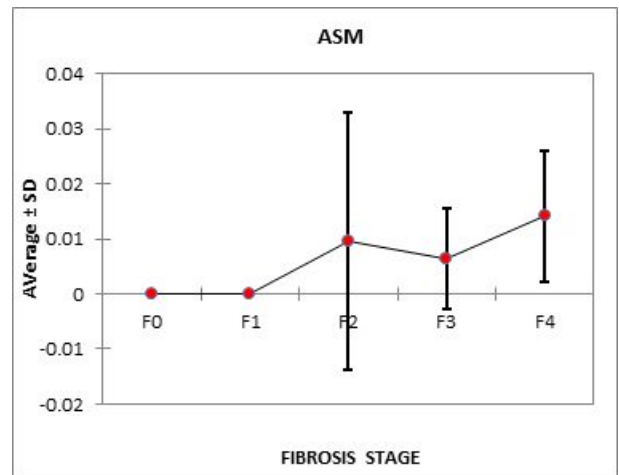


Fig.9. Comparison of ASM according to FS

Contrast values had significant differences between F0 and F1 versus, F2, F3 and F4, the lower grades having lower contrast values.

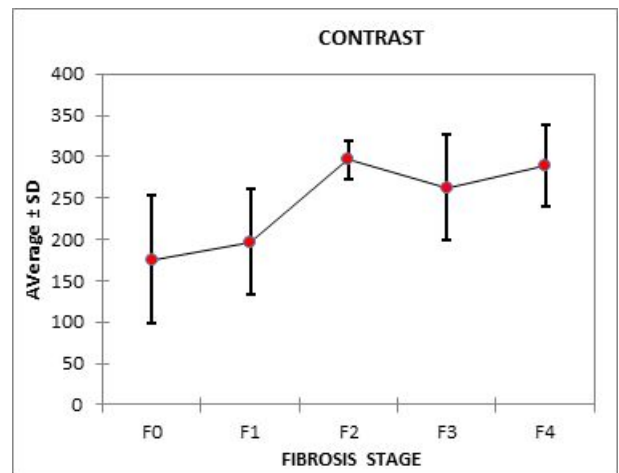


Fig.10. Comparison of CONTRAST according to FS

There were no significant differences for Correlation values among different fibrosis stages.

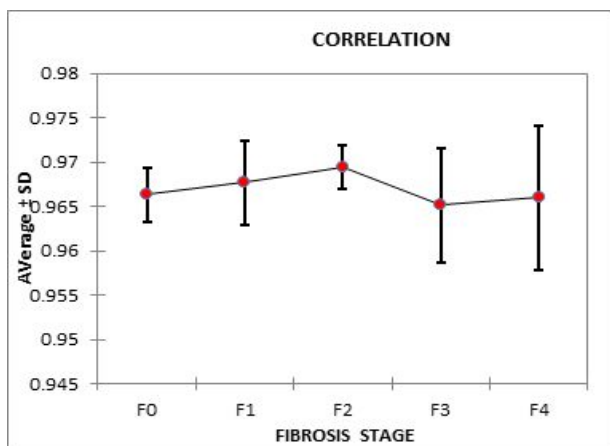


Fig.11. Comparison of CORRELATION according to FS

value and directly related with SD%, AREA, COMP, Skewness, IDM, ASM and Contrast.

Table 2. Correlation analysis

Parameter	Pearson r	p	Significance
MEAN	-0.694	< 0.0001	HS
SD	0.564	< 0.0001	HS
%AREA	0.737	< 0.0001	HS
COMP	0.590	< 0.0001	HS
KURT	0.106	0.409	NS
SKEW	0.631	< 0.0001	HS
ENT	0.034	0.791	NS
IDM	0.527	< 0.0001	HS
ASM	0.436	0.000	HS
CONT	0.580	< 0.0001	HS
CORR	-0.082	0.524	NS

We calculated Pearson correlation coefficient between each parameter and the FS value. Fibrosi stage is inversely related to the MEAN

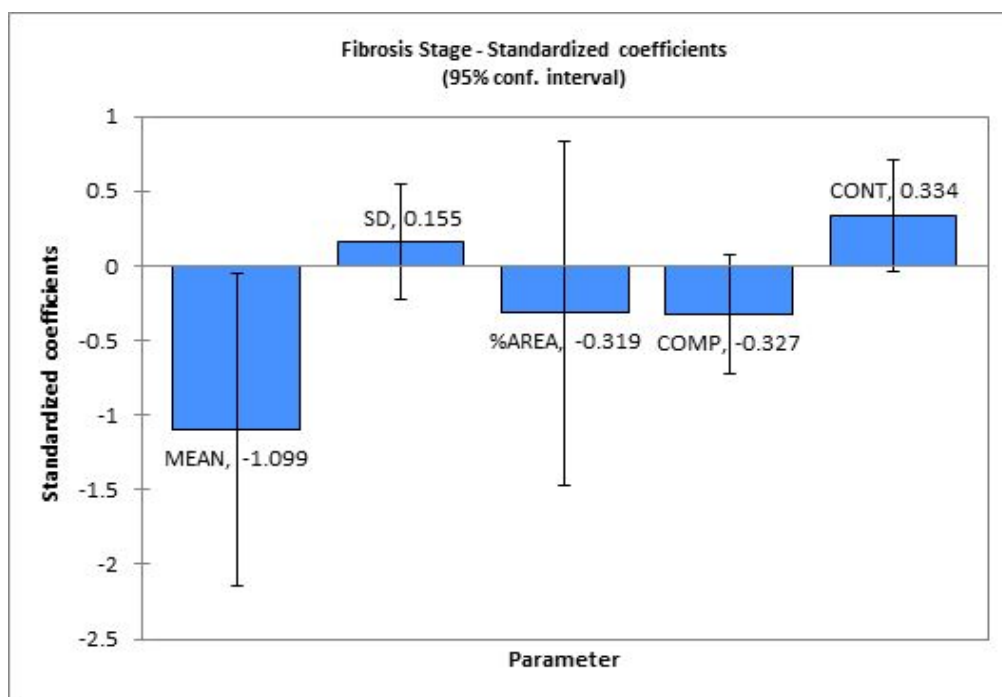


Fig.12. Standardized coefficients for the multivariate analysis of Fibrosis Stage

The results of the analysis of the influence of the recorded parameters on the score for FS was that MEAN had a major impact in FS determination, being the only parameter where we found p<0.5.

Table 3. Multivariate analysis for FS evaluation

Parameter	Value	Standard error	p
MEAN	-1.099	0.523	0.040
SD	0.155	0.193	0.426
%AREA	-0.319	0.576	0.581
COMP	-0.327	0.200	0.107
CONT	0.334	0.186	0.079

While verifying multiple mathematical methods which would have made possible to estimate various elastographic parameters through multivariate linear regression we reached the next equation with minimal levels of error.

$$FS = 10.478 - 0.091 * MEAN + 0.021 * SD - 0.031 * \% AREA - 0.037 * COMP + 0.007 * CONT$$

## Discussion

The need of new methods in assessing liver fibrosis through non-invasive imagistic methods has been related so far with ultrasonography and MRI. While a liver biopsy represents 1/50.000th of the entire organ, which may lead to repeated procedures or under-staging [13], ultrasound-based techniques have been evaluated so far with promising results. According to the available data in the literature, as well as the fact that TE is a validated imagistic method by European US societies we have considered suitable to use it as the reference method in our study. Also the latest cut-off values proposed in the Tsochatzis meta-analysis were considered the basis of fibrosis assessment in staging differentiation.

RTSE has been evaluated so far with success in different organs, however in liver fibrosis assessment it has been put aside for some time, due to some drawbacks such as inconsistency between the US-systems or data analysis. Owing to evolving field of medical devices, with the development of RTSE – HI VISION Preirus system (Hitachi Medical Systems Europe Holding AG), the technique has evolved and specific elastographic parameters have been evaluated into a specific fibrosis index. This index is an evolution of the tissue mean elastography calculation of the histogram analysis containing the mean value and standard deviation of pixels within a selected ROI along with secondary parameters. In 2012 Wang J et al. [14] analyzed the elastic index of patients with chronic hepatitis B using 11 parameters from the elastogram. He was soon followed by Colombo et al. 15 who compared TE and ARFI, with the same RTSE technology.

Patient's examination was done by experienced investigators who had no previous knowledge of TE results. The received data was recorded with the standard probe along the intercostal spaces, based on the heartbeat movement, with no compression what so ever. [16] Also the ROI evaluated within the elastogram did not contain any intrahepatic vessels, therefore avoiding potential

elastograms artifacts that may influence the results. [17]

The LFI by RTSE has been found relevant for advanced hepatitis and early cirrhosis in patients with viral chronic hepatitis. [18] Nonetheless this is considered important because of the special attention required for antiviral treatment proposal. Our study showed that the LFI related to RTSE was significant in high stage fibrosis differentiation, with the MEAN parameter having the major impact in fibrosis stage determination. The Pearson correlation coefficients and the fibrosis stage showed high significant statistics significance ( $p < 0,001$ ) with the SD, % AREA, COMP, Skewness, IDM, ASM and Contrast proportionally direct with the fibrosis stage and with the MEAN inversely related. These results confirm the fact that RTSE might be efficient in assessing fibrosis when compared TE results. An important link was observed between the fibrosis stage and the decreasing elastic ratio, correlation which was also studied by Kanamoto et al. [19]. As a result our study confirms that RTSE can differentiate advanced fibrosis which comes in hand with important therapeutic value.

The main limitation of the study can be considered the absence of histopathological evaluation. With liver biopsy being excluded from therapy guidelines in Europe, liver fibrosis staging with only imagistic methods might be considered a disadvantage. On the other hand, a larger number patients would have been necessary to support our study results.

Our data provides valuable information on RTSE fibrosis assessment. The prospective nature of our study and the fact that the evaluation was conducted by experienced practitioners supports our data. Also the fact that both procedures were performed the same day with minimum time distance between examinations confirms that the patient's status was not changed. Additionally a great advantage can be considered the fact that all patients included in the study had viral chronic disease of different stages.

## Conclusions

There is no doubt that imagistic methods of assessing liver fibrosis are of special interest in chronic liver fibrosis assessment. RTSE comes as a potential new technology based on elastogram evaluation which may prove to be more efficient along with larger prospective studies. As a strong incentive to the research of elastographic area, RTSE should be taking into



considerations further on as the need of new painless and cost-effective procedures are in need.

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*Corresponding Author: B.S. Ungureanu M.D., First Clinic of Internal Medicine, Department of Gastroenterology, Clinical County Emergency Hospital of Craiova, Tabaci 1, Craiova 200638, Romania;  
Tel: +40 723 178 763, e-mail: boboungureanu@gmail.co*