Non-invasive Steatosis Assessment through the Computerized Processing of Ultrasound Images: Attenuation versus First Order Texture Parameters

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Abstract—**Steatosis is a frequent histological finding in patients with chronic hepatitis C virus (VHC) infection. Usual ultrasonography (US) cannot accurately detect the steatosis grade, nor can it always discriminate between steatosis and fibrosis. An improvement of usual US examination is currently under research. A possible approach might be the computerized processing of the data comprised in the US image. In the present paper we set out to compare the performance of two computerized methods for the steatosis assessment on the US images: the attenuation coefficient and the first order textural parameters (FO): Mean, Standard Deviation and Skewness. The attenuation coefficient correlated significantly with steatosis (r=-0.444, p<0.0001), but not with fibrosis (r=-0.046, p=0.395) or necroinflammatory activity (r=-0056, p=0.211). Of the FO parameters, only the FO mean correlated significantly with steatosis (r=0.300, p<0.0001), but also with necroinflammatory activity (r=0.128, p=0004). The present study proves that, in patients having chronic hepatitis C, the attenuation coefficient, but also the FO mean, can discriminate between different steatosis grades; however, the attenuation coefficient has a better performance than the FO mean, being influenced only by steatosis, not by fibrosis or necroinflammatory activity. The area under the ROC curve is significantly better for the attenuation coefficient as compared to the FO mean for the prediction of steatosis regardless of the grade (0.741 vs 0.652, p=0.001), as well as for the prediction of moderate/severe steatosis (0.791 vs 0.719, p=0.043).**

Keywords— **steatosis, chronic hepatitis C, noninvasive, computerized methods, ultrasonography**

I. Introduction

Hepatic steatosis is a frequent histological finding in patients with chronic hepatitis C virus (VHC) infection, occurring in more than 50% of cases [1]. There is increasing evidence that steatosis is an independent risk factor associated with liver necroinflammatory activity and progression of fibrosis in patients with chronic HCV infection [2]. Therefore, reliable and early diagnosis of hepatic steatosis is crucial to monitor disease progression and therapeutic intervention. The gold standard for assessing diffuse liver disease, including steatosis, is liver histology. However, liver biopsy is an invasive procedure associated with potential complications, as well as sampling error and interobserver variability [3].

Hence, reliable non-invasive methods to assess steatosis in patients with chronic HCV infection are needed. Among these, imaging methods have an important role, and of them, ultrasonography (US) is the best choice from the point of view of the cost, accessibility and lack of side effects. The ultrasonic alterations of fatty liver appear when the fatty load of the hepatocytes exceeds 15–20%. These alterations are represented by hepatomegaly, increased parenchymal echogenicity ("bright liver"), attenuation of the ultrasounds in the subcapsular strata, difficult visualization of the portal vein walls, of the gallbladder wall and of the hepatic capsule, the apparent dilatation of the vessels (especially of the suprahepatic ones) and the false transonic aspect of the parenchyma of the right kidney as opposed to that of the liver. However, the performance characteristics of conventional grey-scale US may vary considerably among studies, ranging from good to poor [4]. One reason might be that concomitant liver pathology (inflammation, fibrosis) may alter the ultrasonographic diagnosis of steatosis [5]. Fibrosis may also appear hyperechoic, but most of the time, fibrosis and fatty infiltration coexist, which is why the term "fatty-fibrotic pattern" is used to define the resulting aspect [6]. It is for this very reason that an improvement of usual ultrasonographic examination is currently under research. A possible approach might be the computerized processing of the data comprised in the ultrasonic image, taking into consideration that all the information concerning the characteristics of the tissue already exist in the echoes returned by the transducer. This is based on the principle according to which the pathological tissular modifications due to a specific disease (such as steatosis or fibrosis) lead to alterations of the physical and micro architectural features (density, thickness, elasticity, homogeneity, etc.). These are very difficult to visualize, but, because they affect the propagation of ultrasounds, they can be perceived through the complex image analysis (the ultrasonic tissular characterization) as a different textural pattern from the healthy one [7]. The ultrasonic tissular characterization can be achieved either by methods based on the study of parenchymal echogenicity and on the attenuation of the

ultrasounds (attenuation and backscattering coefficients), or by methods based on the quantification of some textural parameters [8-10].

We have proven in our previous research that, between the attenuation and backscattering coefficients, the attenuation coefficient has the best performance in the assessment of steatosis in nonalcoholic steatohepatitis (NASH) patients [11]. Furthermore, the attenuation coefficient is also superior to biochemical methods (such as adiponectin) for the non-invasive assessment of steatosis [12]. At the same time, the attenuation coefficient performs better than the textural parameters derived from the gray level co-occurrence matrix (GLCM) in NASH patients. However, of all tested textural parameters, only the entropy computed on GLCM only correlates to steatosis; even then, it only discriminates between a normal aspect and NASH, but not between grades of steatosis [13].

In the present paper we set out to compare the performance of two computerized methods for the steatosis assessment on the ultrasonographic images in chronic hepatits C patients: the attenuation coefficient and some textural descriptors based on the first order (FO) statistics.

II. Patients and Methods

A. Patients

526 consecutive patients with chronic HCV infection examined at the 3rd Medical Clinic, University of Medicine and Pharmacy Cluj-Napoca, were prospectively included in this study. All of them were HCV-RNA positive and underwent percutaneous liver biopsy (LB) for the grading and staging of diseases. All patients were referred to an ultrasound exam 1 day prior to LB. Besides the epidemiological data, the following biological parameters were determined for all patients on the same day as LB: aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl-transpeptidase (GGT), total bilirubin, alkaline phosphatase, fasting blood glucose, fasting serum cholesterol and triglycerides. The study was approved by a local ethical committee of the University of Medicine and Pharmacy Cluj-Napoca. The nature of the study was explained to the patients and they each provided written informed consent before the beginning of the study, in accordance with the principles of the Declaration of Helsinki (revision of Edinburgh, 2000).

B. Ultrasound exam

Each studied patient was submitted to an abdominal ultrasound exam by means of a GE Logiq 7 device, using a 5.5 MHz convex probe, one day before the LB. The examination protocol was built so as to acquire the maximum amount of information from the tissue level, with as little „noise" as possible over added to this process. In order not to change the textural elements, the amount of digital post-processing must be as small as possible, and thus, all the post-processing parameters were set at minimum, and in order to exclude movement artifacts, the tissue image „Freeze" took place as quick as possible (by using a „Frame rate" which must be as high as possible). We worked with harmonic (because it increases the quantity of information coming from tissues). The "Time Gain Compensation" curve was adjusted to a neutral position. The device was set so as to stand on all these principles, and once the setting took place, it was used for all the examined patients. For each patient, US images were acquired from the right lobe through intercostals spaces. Depth was set at 16 cm. The images were saved on the ultrasound machine hard disk in DICOM format and further processed using a special soft designed by the Technical University of Cluj-Napoca.

C. Computing the image coefficients

On each US image, a straight line was fitted so as to avoid artifacts. This line represents the ultrasound beam path into the liver tissue and it has to be as parallel as possible to the US rays, preferably vertical. The fitted line is the region of interest (fig.1).

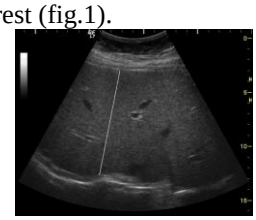

Fig. 1 Ultrasound image from right lobe at 16 cm. The mean gray levels are computed along the white line.

The grey level values for each point along this line are calculated by averaging 7 horizontal pixels (the pixel below the line and three more pixels from each side) [14]. For each point on the line, two values were stored: the average grey level computed as above and the depth (fig.2). As a measure of ultrasonic attenuation, linear regression by least-squares approximation was applied to this dataset. The slope represents the attenuation coefficient.

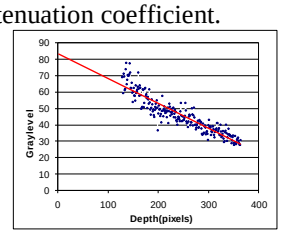

Fig. 2 The graphical representation of the average gray level with respect to depth.

Furthermore, FO parameters were calculated in each patient. The first order parameters employed here belongs to the large family of statistical texture descriptors. The texture is viewed as a collection of pixels, each pixel having a grey level that follows a normal distribution. First order parametrs measure the pixel distributions and report various measures that depend on how much the actual distribution is deviated from the assumed Gauss distribution. In present paper the following coefficients are computed: Mean, Standard Deviation, Skewness. In the following is described how these statistics are computed [15, 16]. First, the histogram of the image is computed. The histogram basically counts how many pixels of each grey level are in the image. Because the grey levels are assumed to follow a Gaussian distribution this histogram should have the classical bell shape. Let *h(i)* be the number of pixels that have a grey value equal to i. Let *p(i)* = *h(i)/N* where *N* are the total number of pixels. We define the following:

Mean:

$$\mu = \sum_{i-0}^{G} ip(i) \quad (1)$$

Standard Deviation:

$$\sigma^2 = \sum_{i-0}^{G} (\mu - i)^2 p(i) \quad (2)$$

Skewness:

$$\mu_3 = \sum_{i-0}^{G} (i - \mu)^3 p(i) \quad (3)$$

It is important to note is that FO Mean represents the mean grey level of the pixels in the image, the FO Standard Deviation measures the width of the histogram (or the contrast). The skweness measures the simmetry of the histogram. If the histogram is assimetrical (i.e. tilted to one side) the skewness will measure this deviation. Skewness is sensitive to the deviations from assumed normal distribution.

These statistics are not computed on the entire image but only on a 64x64 pixels squared region. This region is manually placed on the ultrasound image by a trained radiologist. The area where this region of interest is placed has to be clear of artifacts and as close as possible to the center of the image. Moreover, this squared region should be placed at 1 cm below the upper liver capsule in full liver tissue (fig 3)

D. Histological study

A liver biopsy examination was performed for all the patients. Only biopsy specimens with more than 6 intact portal tracts were eligible for evaluation [17]. Liver fibrosis and necroinflamatory activity were evaluated semiquantitatively according to the METAVIR scoring system [17]. Fibrosis was staged on a 0-4 scale as follows: F0 – no fibrosis; F1 – portal fibrosis without septa; F2 – portal fibrosis and few septa; F3 – numerous septa without cirrhosis; F4 – cirrhosis. Necroinflammatory activity was graded as follows: A0– none; A1 – mild; A2 – moderate; A3 – severe. Steatosis was categorized by visual assessment as: 0- none; 1- steatosis in <33% of hepatocytes; 2- steatosis in 33% to 66% of hepatocytes; and 3- steatosis in > 66% of hepatocytes.

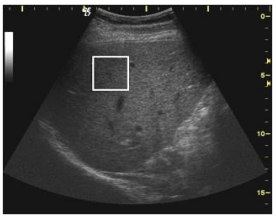

Fig. 3 A squared region of interest established on a right lobe ultrasound image avoiding the major artifacts like blood vessels, shadows, etc.

E. Statistical analysis

The statistical analysis was performed using the SPSS software version 15.0 (SPSS Inc., Chicago, IL, USA). The relationships between the parameters were characterized using the Spearman correlation coefficients. The attenuation coefficient (AC) and FO data were expressed as median values. Differences in mean values were tested by one-way analysis of variance (ANOVA) and Kruskal-Wallis test; The diagnostic performance of AC was assessed using sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), accuracy, likelihood ratios (LR) and receiver operating characteristic (ROC) curves. Optimal cut-off values for AC were chosen to maximize the sum of sensitivity and specificity, and positive and negative predictive values were computed for these cut-off values.

III. RESULTS

526 patients were enrolled in the study with a mean age of 46.79 ± 10.08 years; the majority was women (63.1%). The mean size of the bioptic speciment was 11.10 mm (±2.8), with a mean number of 12.15 (±4.1) portal spaces.

The histopathological analysis found no steatosis in the majority of patients (54.2%), mild seatosis in 34.4% (5-33% fatty content), moderate steatosis in 8% (34-66% fatty content), and severe steatosis in 3.4% (>66% fatty content). Because of the low number of patients in the last two categories, we grouped the patients in 3 groups for further analysis: S0 (patients without steatosis), S1 (patients with

mild steatosis) and S2-3 respectively (patients with significant steatosis, either moderate or severe).

In addition, the patients had different fibrosis stages: no fibrosis - F0 (6.7%), mild fibrosis - F1 (36.1%), significant fibrosis - F2 (33.5%), severe fibrosis - F3 (16.5%) and cirrhosis respectively (F4) (7.2%), and various degrees of necroinflammatory activity: A0 (4.9%), A1 (20%), A2 (51.4%), A3 (23.7%).

A. Correlation between the attenuation coefficients and different histological parameters

The attenuation coefficient correlated significantly with steatosis, but not with fibrosis or necroinflammatory activity. Of the FO parameters, only the FO mean correlated significantly with steatosis but also with necroinflammatory activity (table 1).

We found a significant variability of the attenuation coefficient, but also of the FO mean, in relation to the different steatosis grades (table 2, fig 4)

The area under the ROC curve is significantly better for the attenuation coefficient as compared to the FO mean, for both the prediction of S0 vs S123 and that of S01 vs S23 (table 3, fig 5).

Table 1 Spearman Correlation Coefficient between different coefficients computed on the ultrasound image and steatosis, fibrosis and necroinflammatory activity

	Steatosis		Fibrosis		Necroinflammatory activity	
	r	p	r	p	r	p
Attenuation coefficient	-0.444	<0.0001	-0.046	0.295	-0.056	0.211
FO mean	0.300	<0.0001	0.032	0.468	0.128	0.004
FO standard deviation	0.006	0.897	0.033	0.454	0.065	0.150
FO skewness	-0.075	0.087	0.074	0.090	-0.018	0.686

Table 2 Mean value of the attenuation coefficient and FO mean for different grades of steatosis in HCV patients

	S0 (0-4% fatty content)	S1 (5-33% fatty content)	S2-3 (>33% fatty content)	p
AC	-0.0082±0.065	-0.0586±0.0676	-0.1021±0.0716	<0.0001
FO mean	48.640±10.055	52.917±11.069	58.732±10.404	<0.0001

Table 3 Areas under the ROC curve for the attenuation coefficient and FO mean in the prediction of each steatosis grade

	AUROC for AC	AUROC for FO mean	Difference between AUROCs	Standard error	*p*
S0vsS123	0.741	0.652	0.089	0.026	0.001
S01vsS23	0.791	0.719	0.072	0.036	0.043

Because of the better performance of the attenuation coefficient in the grading of steatosis than that of FO mean, we further tested the performance of the attenuation coefficient in the prediction of steatosis regardless of the grade (S0 vs S123), as well as the prediction of moderate/severe steatosis (S01 vs S23) in HCV patients. The resulting values are displayed in table 4.

Table 4 Attenuation coefficient cutoff values for the diagnosis of steatosis grades ≥ S1 and S2-3

	S 0 vs S 1-2-3	S 0-1 vs S 2-3
AC cutoff value	-0.0471	-0.0564
Se (%)	67.63	86.67
95% CI	61.3-73.5	75.4-94.0
Sp (%)	70.18	64.81
95% CI	64.5-75.4	60.3-69.1
+LR	2.27	2.46
-LR	0.46	0.21
PPV	65.7	24.1
NPV	71.9	97.4
AUROC	0.741	0.791
SE	0.021	0.025
95% CI	0.700-0.777	0.754-0.825

IV. Discussions

An ever-developing field of research is the non-invasive assessment of steatosis occurring in diffuse liver diseases. Of all non-invasive methods, ultrasonography plays an important part thanks to its widespread availability and relatively low cost. However, usual ultrasonography has its limitations: it cannot accurately detect the steatosis grade, nor can it always discriminate between steatosis and other histopathological alterations frequently occurring in diffuse liver diseases (such as inflammation or fibrosis). This justifies the constant attempt to improve the ultrasonographic examination, one method being the computerized processing of images (ultrasonic tissular characterization). The ultrasonic tissular characterization can be achieved by methods based either on the study of parenchymal echogenicity and on the attenuation of the ultrasounds (attenuation and backscattering coefficients), or on the quantification of some textural parameters [8, 9].

Gaitini et al [9] tried to compare textural to attenuation/backscatter indices to suggest the better approach for an objective noninvasive ultrasonic “biopsy”.

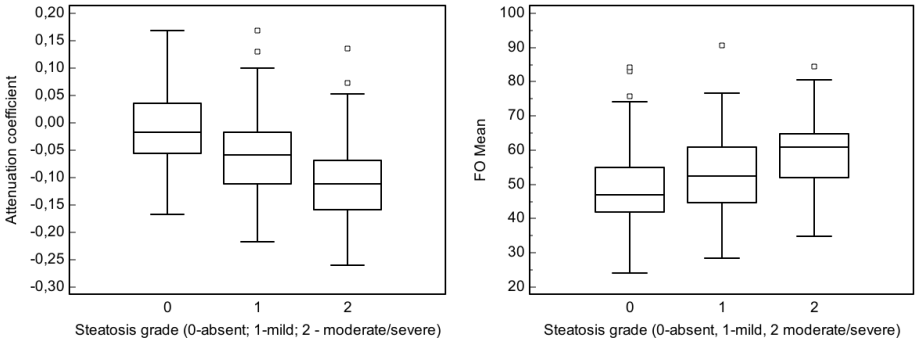

Fig. 4 Values of attenuation coefficient and FO mean according to different grades of steatosis (median and interquartile ranges)

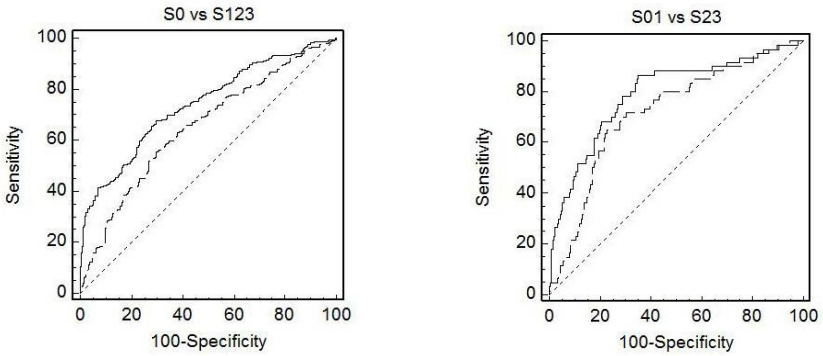

Fig. 5 ROC curves for the attenuation coefficient (continuous line) and FO mean (fragmented line) used for the prediction of each steatosis grade: S0 vs S1-2-3; S0-1 vs S2-3

The attenuation/backscatter indices were superior to textural indices in differentiating between the categories studied. By using the attenuation coefficient, Gaitini [20] obtained an ideal area under the ROC curve (AUROC=1) for the differentiation of patients having „pure" steatosis (without superimposed inflammation of fibrosis) from the healthy liver, but, the patients without severe steatosis had been excluded from that particular study. This approach has, however, a rather limited practical value since the ultrasonographic changes of severe steatosis can be discriminated from the normal liver by the „classic" examination.

Some authors [18] suggest that steatosis can be detected through imaging methods when it is moderate or severe (>33%). In the present study we have found AUROCs of 0.741 and 0.791 respectively for the prediction of the presence of steatosis and respectively for the prediction of moderate/severe steatosis. Such discrimination could not have been possible through the visual inspection alone, especially since these patients have, alongside steatosis, other histologic alterations that may distort the ultrasonographic image (fibrosis, inflammation or ballooning).

In the context of co-existing steatosis, necroinflammatory activity and fibrosis, first of all we wanted to see how much the attenuation coefficient and FO parameters were influenced by the histopathological aspects found in patients with VHC infections. The attenuation coefficient in patients with VHC was found to correlate significantly with steatosis, but there was no significant correlation with activity or fibrosis. This finding might be the first step in the further study of this coefficient used for the differentiation between steatosis and fibrosis on the ultrasonic image. In exchange, the FO mean is influenced by both steatosis and necroinflammatory activity.

Webb et al [19] have also tried to quantify the intrahepatocyte fat content by using the hepatorenal index, defined as the difference between the echogenicity of liver and that of the right kidney. The main limitation of this approach is the reference system (the kidney), whose echogenicity could also be altered by intrinsic conditions. On the other hand, the parameter quantified in these cases is the echogenicity of the liver and kidney respectively; the echogenic pattern of the liver can also result from superimposed fibrosis or inflamation, not only steatosis. In the present study we have proven that the attenuation coefficient correlates only to steatosis, not with

inflammation or fibrosis, while the FO mean correlates both to steatosis and inflammation. Indeed, the performance of the attenuation coefficient was better than that of the FO mean, both for the prediction of steatosis (regardless of the grade), as well as for the prediction of moderate steatosis, at least.

The FO Mean parameter measures the average grey level intensities in the designated area. Knowing that, for an ultrasound image, a higher intensity means higher amplitude of the receiving echo one can assume that a higher value for "FO Mean" means that the underlying tissue has an enhanced echogeneity. This echogeneity, in the case of parenchimatous organs can be explained by the presence of numerous but small interfaces. This phenomenon has been observed by many authors in the case of steatosis, so, the correlation of FO Mean with the steatosis is not a surprise. In the case of necroinflamatory activity the liver tissue suffers a local swelling, hence the densities varies and produces numerous interfaces. The other parameters from FO statistics are not sensible to global changes to the image characteristics but to relative changes between pixels. It seems that liver steatosis can be detected only using a global measure of the ultrasound behaviour. A method that focuses only on a small region is less sensitive to steatosis alterations (AUROC for attenuation is better than AUROC for FO Mean)

In conclusion, the present study proves that, in patients having chronic hepatitis C, the attenuation coefficient, but also the FO mean, can discriminate between different steatosis grades; however, the attenuation coefficient has a better performance than the FO mean, being influenced only by steatosis, not by fibrosis or necroinflammatory activity.

ACKNOWLEDGMENT

This work was funded by the Romanian Authority for Scientific Research through the CEEX Program [grants nr 71/2006 and 94/2006] and the 2007-2013 National Program for Research, Development and Innovation [grant PNCDI2-Partnership nr 41-071/2007]

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