Optimal Elasticity cut-off value for discriminating Healthy to Pathological Fibrotic patients employing Fuzzy C-Means automatic segmentation in Liver Shear Wave Elastography images

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Abstract. The aim of the present study is to determine an optimal elasticity cut-off value for discriminating Healthy from Pathological fibrotic patients by means of Fuzzy C-Means automatic segmentation and maximum participation cluster mean value employment in Shear Wave Elastography (SWE) images. The clinical dataset comprised 32 subjects (16 Healthy and 16 histological or Fibroscan verified Chronic Liver Disease). An experienced Radiologist performed SWE measurement placing a region of interest (ROI) on each subject’s right liver lobe providing a SWE image for each patient. Subsequently Fuzzy C-Means clustering was performed on every SWE image utilizing 5 clusters. Mean Stiffness value and pixels number of each cluster were calculated. The mean stiffness value feature of the cluster with maximum pixels number was then fed as input for ROC analysis. The selected Mean Stiffness value feature an Area Under the Curve (AUC) of 0.8633 with Optimum Cut-off value of 7.5 kPa with sensitivity and specificity values of 0.8438 and 0.875 and balanced accuracy of 0.8594. Examiner’s classification measurements exhibited sensitivity, specificity and balanced accuracy value of 0.8125 with 7.1 kPa cutoff value. A new promising automatic algorithm was implemented with more objective criteria of defining optimum elasticity cut-off values for discriminating fibrosis stages for SWE. More subjects are needed in order to define if this algorithm is an objective tool to outperform manual ROI selection.

1. Introduction
Chronic Liver Disease (CLD) is considered as the only major cause of death still increasing year-on-year, causing more deaths than diabetes and road accidents combined [1]. For this reason the correct estimation of the disease progress towards a suitable treatment is considered very important.
Liver Biopsy (LB) plays an important part of patient evaluation to various liver diseases. Besides establishing the diagnosis, the biopsy is often used to assess the severity of the disease in terms of both grade and stage. Staging in most chronic liver diseases relates to the degree of scarring (fibrosis) with cirrhosis with its clinical complications being the final stage [2]. Although LB is still considered as...
'gold standard' for estimating the progress of CLDs it has many important limitations. It is invasive and can cause significant complications. Nearly 30% of patients report having substantial pain after liver biopsy, and some experience serious complications such as pneumothorax, bleeding, or puncture of the biliary tree. In rare cases, patients die of bleeding. Furthermore, hepatic pathology, particularly fibrosis, is not always uniformly distributed. Surgical wedge biopsy provides adequate tissue volume to overcome this problem.

Needle biopsy, on the other hand, provides a much smaller volume of tissue (1/50,000 of the total liver mass) [3]. Obviously, needle liver biopsy is far from an ideal test. Liver diseases can be diagnosed precisely with laboratory tests, imaging studies, or both. Thus, needle liver biopsy is playing a lesser role in diagnosis.

Conventional imaging techniques cannot provide information about tissue mechanical properties. Many injuries can cause changes in tissue stiffness, especially tumors and fibrosis. In recent years, various non-invasive ultrasound methods have been developed to study tissue elasticity for a large number of applications [4].

The ultrasound based elastographic methods used for liver fibrosis assessment can be divided into two main categories: strain elastography (or quasi-static elastography) – in which tissue excitation is performed manually or using the cardiac motion; and shear wave elastography – in which tissue excitation is induced either by ultrasound waves produced by the probe (for elastographic methods integrated into a standard ultrasound system: Acoustic Radiation Force Impulse Elastography and Real Time 2D-Shear Waves Elastography), or induced by a mechanical impulse (thump) generated by a coaxial vibrator (for Transient Elastography).

Shear wave elastographic methods include: Transient Elastography (TE), Acoustic Radiation Force Impulse (ARFI) quantification Elastography and Real Time 2D-Shear Waves Elastography (2D-SWE) [5].

TE is the oldest shear wave elastographic method, used for liver fibrosis evaluation in various liver diseases. The usefulness of TE for liver fibrosis assessment was confirmed by meta-analyses studies. ARFI elastography was more recently developed with data published in the last years showing that it is a useful tool for fibrosis evaluation, non-inferior to TE. SuperSonic Shear Imaging (2D-SWE) is the latest developed shear waves elastographic method with few but promising data being available until now [5-6].

Most approaches on literature try to set cut-off values to correspond elasticity values to fibrosis stages according to Metavir Classification. The clinical protocol used depends on taking the mean number value of successive liver measurements of tissue elasticity from the same intercostal space. ROC analysis is performed then on all the mean elasticity values from all patients to obtain the best cut-off values which delimit Elasticity values ranges that correspond to Metavir Fibrosis Stages [5-6].

This approach shows relatively good results for the best cut-off values (0.8-0.85 AUC) but has quite serious limitations. The examiner places a Region of Interest (ROI) superimposed on B-Mode Ultrasound on a suitable area of liver parenchyma which shows the stiffness of the liver by applying elasticity values to a color map (low stiffness: blue, high stiffness: red) so that there is a color specification for liver stiffness for the examiner to take successfully the measurement. This measurement is taken by placing a circular shaped index in the ROI to take the mean stiffness of the area inside the circular index [5-6].

This method relies on the examiner’s opinion of where is the most representative area of liver parenchyma to take the measurement. This means that the method is subjective to the examiner’s criteria who in most cases uses prior knowledge of patient’s clinical history, blood serum markers, or histological examination. For example a patient with a clinical history of cirrhosis provokes the examiner to choose stiffer values as most representative. This also leads to significant Inter- and Intra-observer variability.

The other issue about this method is that takes only two features of the histogram of the elasticity values (Mean and Standard Deviation) and doesn’t take advantage of the rest information that lies in the image. As even an experienced Radiologist cannot notice every detail or factor on the image that
could assist in diagnosis, the role of an automatic system that can calculate the most significant features of an image for diagnosis is very important.

Only one automated approach towards this direction has been done [7]. The study’s main purpose was to estimate how factors such as stability of an area in time and low heterogeneity define areas that their mean values can improve the reliability and reproducibility of SWE using the proposed method. Our study tries to define factors that are important to estimate fibrosis stage from elasticity measurements and make a semi-automated system that prognoses accurately the corresponding fibrosis stages. This is done by segmenting the elastographic image to clusters with low heterogeneity and choosing the cluster with maximum number of pixels. Then the mean stiffness value of the chosen cluster is calculated and is used for ROC analysis to define best cut-off values.

As our data consists of few patients preliminary results are presented and only healthy subjects with no fibrosis (F0) are discriminated from patients with CLD (F1, F2, F3, F4).

2. Materials & Methods

2.1. Clinical Data
Our clinical material consisted of 32 subjects (16 healthy (F0) and 16 with CLD (F1, F2, F3, F4)) who were examined by an experienced radiologist. All SWE measurements were performed in the right lobe of the liver using an appropriate intercostal space. The distance probe / ROI was 3-6 cm. All SWE measurements were performed on a homogenous B-Mode Ultrasound image with no Ultrasound visible vessels. A normal inspiration was established for diaphragm stabilization assuring liver’s immobility. When an imperfect skin/probe contact was observed, an acoustic coupling medium (pad) was interposed to assure a perfect acoustic transmission.

When a SWE image could not be obtained using an intercostal space, the left lobe of the liver was used for SWE measurements. In both circumstances perfect immobility of the liver parenchyma and minimum disturbance from heart’s compression were assured.

Two SWE images for each subject were saved, one with no markings on the elastogram for testing the proposed method and one with the radiologist’s stiffness measurement using the standard protocol that is provided by the SSI Aixplorer and that is providing the mean value of a circular ROI placed on the elastogram Q-Box superimposed on B-Mode Ultrasound image.

All healthy subjects had normal Biochemical Markers and with no abnormal liver findings during their Ultrasound examination. All CLD patients performed liver biopsy and histological examination for fibrosis stage estimation by a senior histopathologist for validation purposes.

2.2. Automatic ROI Detection
SWE elastogram images with no markings were segmented by means of Fuzzy C-Means (FCM) unsupervised clustering, utilizing 5 clusters for each image. Mean Stiffness value and pixels number of each cluster were calculated using Aixplorer’s colormap for inverting RGB values to stiffness values. The mean stiffness value feature of the cluster with maximum pixels number was then fed as input for ROC analysis.

3. Results
The selected Mean Stiffness value feature an AUC of 0.8633 (Figure 1) with optimum Cut-off value of 7.5 kPa for F≥F1 with Sensitivity and Specificity values of 0.8438 and 0.875 and Balanced Accuracy of 0.8594. Automatic ROIs sizes defined by the proposed algorithm ranged from 0.5-0.8 of the whole elastogram.
Examiner’s classification measurements exhibited Sensitivity, Specificity and Balanced Accuracy values of 0.8125 with 7.1 kPa cut-off value.
4. Discussion
A new promising automatic algorithm was implemented with more objective criteria of defining optimum elasticity cut-off values for discriminating fibrosis stages for SWE. The objectivity of the proposed method is achieved by defining standard criteria (maximum size homogeneous area) that discriminate more accurately Metavir fibrosis stages than the existing methods. This could lead to a software that selects and takes measurement automatically from a suitable area or propose an area for the examiner to take measurement with the existing circular ROI. As a next step for research purposes, a study with two radiologists taking two measurements each, by the same proposed area could evaluate if the proposed method improves intra- and inter-observer variability achieving better accuracy from the existing method. More subjects are needed in order to discriminate between all fibrosis stages and to define if this algorithm is an objective tool to outperform manual ROI selection.

5. References
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