The Combination of Shear Wave Elastography and Elf Test in a Single Score Improves the Diagnostic Specificity for Liver Fibrosis Prediction

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Abstract

**Background.** Chronic liver diseases (CHDs) are an important public health issue. The presence of significant fibrosis is a hallmark for liver disease staging and prognosis.

**Aims.** To develop a non-invasive score that can discriminate between patients with or without fibrosis in the aim to avoid liver biopsy.

**Methods.** Forty patients with CHDs who received liver biopsy to stage fibrosis and 12 normal subjects performed also share wave elastography (SWE) and ELF-test. We chose two different outcome for histological fibrosis (F0-F1 vs F2-F4) and (F0-F2 vs F3-F4). ELF-test and SWE were independent predictors, categorized using ROC analysis. Two scores called SCORE1 and SCORE2 were devised.

**Results.** The discriminatory values for SCORE1 were SWE>5.62 kPa and ELF-test >9.33 and for SCORE2 were SWE>7.04 kPa and ELF-test 9.33. SCORE1 specificity was 91.7% (CI 77.5-98.2%), significatively greater than obtained using SWE 63.9% (CI 46.2-79.2%; p=0.0013) or ELF-test 83.3% (CI 67.2-93.6%; p=0.1760) separately. SCORE2 specificity was 95.2% (CI 83.8-99.4%). This value was not-significatively greater than obtained using SWE or ELF-test 81.0% (CI 65.9-91.4%; p=0.0921) separately.

**Conclusion.** SWE and ELF-test can be performed for non-invasive staging of liver fibrosis. Their use grouped in a single score increase the specificity for the prediction of histological fibrosis stage.

Introduction

The worldwide increase in the incidence of chronic liver disease (CLD) is closely related to broader adoption of NAFLD and the metabolic risk factors such as obesity, type 2 diabetes and dyslipidemia. The global prevalence of NAFLD, the major cause of CLD in the occidental world, is currently estimated to be 24% (1), of which one fifth progressing to liver cirrhosis (2). Advanced fibrosis has been identified as the most important histological feature associated with poor outcomes (2) (3). The gold standard for the diagnosis and staging of NASH and fibrosis is the liver biopsy that is an invasive procedure, with a risk for major complications in 1–3% (4). Biopsy also presents several limitations: is dependent on the subjectivity and experience of the pathologist, has sampling problems, which results in misdiagnosis in up to one third of the patients (5), and it show less than 1:50,000 of the total volume. Early diagnosis, dynamic evaluation, and effective treatment can halt or even reverse the progression of liver fibrosis. Identifying the stage of fibrosis is therefore an essential requirement for timely diagnosis and therapy (6).

Many efforts have been made to develop non-invasive methods to diagnose and quantify hepatic steatosis and to be able to predict the degree of fibrosis. Some of these methods are based on medical imaging techniques and biochemical tests.

Shear Wave Elastography (SWE) uses measurement of the propagation velocities of acoustically generated shear waves in tissue to estimate liver stiffness with the benefit of simultaneous anatomical B-Mode ultrasound imaging. This method is becoming an important clinical measure for the identification
of the stage of hepatic fibrosis (7) and its use is also recommended by the clinical guidelines published by the European Federation of Societies for Ultrasound in Medicine and Biology (8) and by the World Federation for Ultrasound in Medicine and Biology (9).

Also serum biomarkers and, in particular, the combined use of three serum biomarkers of hyaluronic acid (HA) (10), tissue inhibitors of metalloproteinases (TIMP-1) (11) and terminal amino-yl propeptide of type III procollagen (PIIINP) (12) has recently been proposed for the detection of fibrosis. This simplified version of the panel of these biomarkers was called Enhanced Liver Fibrosis (ELF) -test (13). This non-invasive test has been shown to possess high reproducibility and good diagnostic performance in assessing the degree of hepatic fibrosis (14) (15). The aim of our study was to evaluate the usefulness of the combined use of ELF-test with SWE to diagnose the presence of absence of hepatic fibrosis and to stage the degree of this pathology.

**Material And Methods**

**Subjects**

In our outpatient clinic, we evaluated 40 subjects with chronic liver disease (patients) who received liver biopsy and 12 normal subjects (2–4). The exclusion criteria were other active infectious diseases or pregnancy. Five patients (12.8%) received a diagnosis of liver cirrhosis, 11 patients (28.1%) were diagnosed with viral chronic hepatitis, 7 (17.9%) had alcoholic liver disease and 17 patients (41.2%) exhibited unexplained abnormalities on their liver test results. None of the normal subjects had a history of liver disease and had normal test results; all of them had a normal abdominal ultrasonography. All of the subjects received a general abdomen US and Shear Wave Elastography (SWE) examination. The study was approved by the local Ethical Committee of the faculty of Medicine of the University of Naples Federico II. The patients provided written informed consent before the beginning of the study.

**HISTOPATHOLOGICAL ANALYSIS**

A liver specimen was collected with the BIOMOL-16 G, a soft tissue biopsy semiautomatic needle (HS SpA. Aprilia-Italy), using the modified Menghini needle technique. The liver biopsy specimens were fixed in formalin and embedded in paraffin. A specialized pathologist with more than 20 years of experience who was blinded to the SWE values and clinical information reviewed the biopsy specimens. Only biopsy specimens 2 cm long and with a minimum of 11 intact portal tracts were eligible for evaluation (6). Liver fibrosis was evaluated semi-quantitatively according to the Metavir scoring system (7). Liver fibrosis was staged using a five-point ordinal scale ranging from 0 to 4 as follows: F0 - no fibrosis; F1 - portal fibrosis without septa; F2 - portal fibrosis with few septa but intact architecture; F3 - numerous septa with architecture distortion without cirrhosis; F4 - cirrhosis. (8). Moreover ALT levels were used as index of hepatic inflammation.

Clinical and demographic characteristics of patients and normal subjects are summarized in Table 1.
Table 1
Demographic and clinic characteristics of patients and healthy subjects.

| Characteristic                  | Patients (39) | Healthy subjects (12) |
|--------------------------------|---------------|-----------------------|
|                                | Number (%)    | Number (%)            |
| Male gender                    | 22 (56%)      | 3 (25%)               |
| Aetiology of liver disease     |               |                       |
| HCV                            | 4 (10.2%)     |                       |
| HBV                            | 7 (17.9%)     |                       |
| Alcohol-related                 | 7 (17.9%)     |                       |
| NASH                           | 2 (5.1%)      |                       |
| Others                          | 19 (48.7%)    |                       |
|                                | Median (range)| Median (range)        |
| Age (years)                    | 48.5 (20.0–78.0) | 27.5 (25.0–48.0)    |
| Weight (kg)                    | 72.0 (51.0–130.0) | 58.0 (52.0–70.0)    |
| Body Mass Index (kg/m²)        | 25.6 (17.9–38.4) | 22.2 (18.8–25.0)    |
| Abdominal circumference (cm)   | 98.0 (77.0–120.0) | 89.0 (79.0–93.0)   |
| AST (U/l)                      | 37.5 (14.0–377.0) | 15.5 (14.0–17.0)   |
| ALT (U/l)                      | 51.5 (9.0–577.0)  | 11.0 (9.0–13.0)     |
| GGT(U/L)                       | 81.0 (14.0–856.0) | 12.5 (10.0–15.0)   |
| Cholesterol (mg/dl)            | 180.0 (62.0–342.0) | 151.5 (133.0–170.0) |
| Triglycerides (mg/dl)          | 120.0 (33.0–353.0) | 37.5 (27.0–48.0)   |
| Shear wave wlastography        | 6.15 (3.14–16.66) | 4.49 (2.92–7.32)   |
| ELF TEST                       | 9.12 (7.66–13.39) | 4.48 (2.92–7.32)   |

**SHEAR WAVE ELASTOGRAPHY**

The Shear Wave Elastography were performed using the iU22 ultrasound system (Philips Healthcare. Bothell, WA. United States) with a convex broadband probe and the ElastPQ® technique. The SWE technique generates shear waves inside the liver using radiation force from a focused ultrasound beam. The patient was lying in a lateral decubitus position with the right arm extended above the head; this to access to the right hypochondrium and to increase the intercostal acoustic window (9–11). The probe was placed parallel to the intercostal space with sufficient gel to minimize rib shadowing. A ROI with a box size of 2.0x1.0 cm² was positioned within the liver parenchyma under visual control in two-
dimensional B-mode at a depth of at least 2 cm below the liver capsule in segments 7 or 8 of the liver, taking care to not include large vasculature or biliary structures. The sub-capsular regions that usually contain larger fibrotic content were avoided. During scanning between ribs no pressure was applied to the liver and the patient was asked to stop breathing for a few seconds to minimize motion artefacts. Liver stiffness measurements were performed on the same area of the liver parenchyma. The equipment provides the share wave velocity (m/s) in the ROI as well as the depth at which the measurement was performed. To compute tissue stiffness in kiloPascal (kPa) the shear wave velocity ($v$) was converted into the Shear Modulus ($G$) using the formula

$$G = \rho v^2$$

where $\rho$ is the density of the tissue (kg/m$^3$).

Fifteen measurements were collected at the same location and a report was generated when a success rate of at least 80% was obtained (12) (13). The median of these measurements were used to estimate the degree of liver stiffness for each subject and were correlated with the biopsy Metavir score. The operator was blinded to the results of previous measurements and to biological and histological data.

**ELF TEST 25**

The ELF-test combines three serum biomarkers: Hyaluronic acid (HA), Procollagen III amino terminal peptide (PIIINP) and Tissue inhibitor of metalloproteinase (TIMP-1). These biomarkers are able to identify a quantifiable level of liver fibrosis. To calculate the ELF value, the ADVIA Centaur CP immunochemical analyser (Siemens Healthcare Diagnostics, Germany) was used according to the manufacturer's instructions and the following formula was applied:

$$ELF = 2.494 + 0.846 \ln (C_{HA}) + 0.735 \ln (C_{PIIINP}) + 0.391 \ln (C_{TIMP-1}).$$

Where (C) is the concentrations of the biomarkers and each assay is measured in ng/mL (14–16). All methods were carried out in accordance with relevant guidelines and regulations.

**STATISTICAL ANALYSIS**

Continuous variables were expressed as the median and range. An unpaired non-parametric Mann-Whitney U test was used to compare data from different groups. Categorical variables were expressed as percentages and compared using a chi-square test. A receiver operating characteristic (ROC) curve was calculated (17). The area under the curve (AUC) was used to evaluate test accuracy and the discrimination value was determined by Youden's J statistic (18). Sensitivity and specificity values were computed using the discrimination values as threshold. All of the statistical tests were two-sided and a p-value of 0.05 or less was considered statistically significant. The statistical analysis was performed using MedCalc software version 12.7 (MedCalc Software Bvba. NL).

**Results**
We have chosen to analyse two different outcome for histological fibrosis: (F0-F1 vs F2-F4) and (F0-F2 vs F3-F4). ELF-test and SWE were chosen as independent predictors. These two variables were categorized using results of ROC analysis and in particular using the cut off values. We devised two scores based on these predictors by assigning the value “1” when the value of both predictors exceeded the cut-off value and “0” in all other cases. We called this two novel scores SCORE1 for (F0-F1 vs F2-F4) and SCORE2 for (F0-F2 vs F3-F4).

**SCORE1**

The ROC Curves obtained from ROC Curve analysis using (F0-F1 vs F2-F4) as outcome were showed in Fig. 1. The discriminatory values were for SWE > 5.62 kPa and for ELF-test > 9.33 (Table 2). The specificity of SWE was 63.9% (CI 46.2–79.2%; p = 0.0013) or for ELF-test was 83.3% (CI 67.293.6%; p = 0.1760) (Table 2). The resulting SCORE1, showed in Fig. 1, had a specificity of 91.7 % (CI 77.5–98.2%) significatively greater than obtained using SWE and ELF-test separately (Table 2).

| Parameter                      | F0-F1 vs F2-F4 |
|-------------------------------|---------------|
| **SWE (kPa)**                 | 0.77 (0.63 to 0.88) | 0.75 (0.61 to 0.86) | 0.79 (0.66–0.89) |
| **ELF test**                  | 0.77 (0.63 to 0.88) | 0.75 (0.61 to 0.86) | 0.79 (0.66–0.89) |
| **SCORE1**                    | 0.77 (0.63 to 0.88) | 0.75 (0.61 to 0.86) | 0.79 (0.66–0.89) |

**SCORE2**

The ROC Curves using (F0-F2 vs F3-F4) as outcome were showed in Fig. 2. The discriminatory values were for SWE > 7.04 kPa and for ELF-test > 9.33. The SCORE2 is showed in Fig. 2.

SCORE2 specificity was 95.2% (CI 83.8–99.4%) (Table 3). This value was not-significatively greater than obtained using SWE or ELF-test 81.0% (CI 65.9–91.4%; p = 0.0921) separately (Table 3).
Table 3
Diagnostic performance of Share Wave elastography (SWE), Enhanced Liver Fibrosis test (ELF-test) and SCORE2 using (F0-F2 vs F3-F4) as outcome.

| Parameter                   | F0-F1-F2 vs F3-F4 |
|-----------------------------|-------------------|
| **Parameter**               | **SWE (kPa)**     | **ELF test** | **SCORE2** |
| Cut-off                     | 7.04              | 9.33         |            |
| Area under the curve        | 0.89 (0.78 to 0.96) | 0.84 (0.71 to 0.93) | 0.87(0.74—0.94) |
| Sensitivity (%)             | 88.89 (51.80–99.70) | 88.89 (51.75–99.72) | 77.78 (39.99–97.19) |
| Specificity (%)             | 80.95 (65.90–91.40) | 80.95 (65.88–91.40) | 95.24 (83.84–99.42) |
| Positive Predictive Value (%) | 50.00 (24.65–75.35) | 50.00 (24.65–75.35) | 77.78 (39.99–97.19) |
| Negative Predictive Value (%) | 97.14 (85.08 to 99.9) | 97.14 (85.08 to 99.9) | 95.24 (83.84–99.42) |

**Discussion**

Assessment of liver fibrosis is important in determining prognosis and disease progression in patients with Chronic liver diseases and is need to choose the better treatment to apply. Although liver for determining the degree of liver fibrosis the biopsy is the gold standard, issues regarding invasiveness of this technique and small amount of liver tissue evaluated can limit its applicability and interpretation in clinical practice. To overcome these limitations, non-invasive methods to address liver fibrosis are being increasingly evaluated. These methods include serum markers such as the Enhanced Liver Fibrosis (ELF) test and elastography.

In our previous work, we found that the accuracy of a test based on the SWE was 0.77, in diagnostic liver fibrosis in patient with Metavir stages from F2 to F4, while the accuracy was 0.89 for patient with Metavir stage from F3 to F4 (19).

The aim of this work is to verify if the addition of the information provided by the ELF-test is able to improve the results obtained using SWE alone. To do this, we have built two scores based on the combination by SWE results with of ELF-test results: SCORE1 and SCORE2 realized using Metavir stages from F2 to F4 and to Metavir stage from F3 to F4, respectively.

The diagnostic accuracy obtained with SCORE1 was 0.79, not significantly higher than that obtained using the only SWE, but in return a significant enhancement of specificity was observed 92% vs 64% (p < 0.004). Similar results were obtained with SCORE2: the difference in the diagnostic accuracy was non significant (0.87 vs 0.89) while, an enhancement of specificity although non significant (95% vs 81%, p = 0.092) was observed. Our results are interesting because a highly specific test is to be used in a screening situations. The increased specificity reducing false positive results (20) reduces the number of subjects to
be proposed for invasive diagnostic techniques or unnecessary therapies. Furthermore, a high specificity is also necessary to verify the presence of a disease that has little clinical evidence.

Our study partially confirms results from previously published studies. Katharina Staufer et al (21) have shown that for diagnosis of F2, F3, and F3 plus, respectively, receiver operating characteristic analysis revealed superior diagnostic accuracy of ELF score (AUC 0.85, 0.90, 0.90), FibroMeterV2G (AUROC 0.86, 0.88, 0.89), FibroMeterV3G (AUROC 0.84, 0.88, 0.88), and LSM per protocol (AUROC 0.87, 0.95, 0.91) versus FIB-4 (AUROC 0.80, 0.82, 0.81) or NFS (AUROC 0.78, 0.80, 0.79). Proprietary fibrosis panels and VCTE show superior diagnostic accuracy for noninvasive diagnosis of fibrosis stage in NAFLD as compared to FIB-4 and NFS. Ragazzo et (22) showed good results for ELF with an AUROC of 0.707 and for ARFI an AUROCs of 0.67 for > F2, 0.74 for > F3, and 0.97 for F4.

Trembling PM et al. (23) evaluated performance of ELF and Transient Elastography (TE) in detecting liver fibrosis with reference to liver histology in a cohort of patients with CHB (n = 182), and compared the performance of these modalities. They demonstrated that, in patients with CHB, ELF has good performance in detection of liver fibrosis. Moreover, TE performs better in detection of severe fibrosis.

The main weak point of our work is the sample size. This limitation leads to high confidence intervals and the difficulty of distinguishing between two similar values of specificity or sensitivity. Therefore, further studies will be conducted in order to increase the sample size. This will allow to highlight further significant differences in order to distinguish the different levels of fibrosis. SWE and ELF-test can be performed with comparable diagnostic accuracy for non-invasive staging of liver fibrosis. The use of ELF-test and SWE in a combined score in a screening test increase the specificity for the prediction of histological fibrosis.

Declarations

Ethics approval and consent to participate: The study was approved by the local Ethical Committee of the faculty of Medicine of the University of Naples Federico II. The patients provided written informed consent before the beginning of the study.

Consent for publication: “Not applicable”

Availability of data and materials: “Not applicable”

Competing interests: “The authors declare that they have no competing interests”

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Acknowledgements:
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Figures
Figure 1

Upper panel) Recieving Operating Characteristic (ROC) curve analysis using (F0-F1 vs F2-F4) as outcome.
Lower panel) Diagnostic crosstab for SCORE1 and its representation in bar diagram