Research Article

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

ARFI, FibroScan®, ELF, and their combinations in the assessment of liver fibrosis: A prospective study

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Background & Aims: Our aim was to evaluate a serologic marker (ELF) and two ultrasound-based methods (FibroScan® and ARFI), as well as their combinations, in the assessment of liver fibrosis.
Methods: One-hundred and forty-six patients (87 liver transplant recipients, 59 non-transplant patients) who underwent liver biopsy were prospectively included. We evaluated the diagnostic accuracy of FibroScan®, ARFI, ELF and the combination of ELF with either ARFI or FibroScan®. After analyzing in separate transplant and non-transplant patients, the whole cohort was divided into a training set and a validation set.
Results: ARFI imaging was successfully performed across the whole cohort, while FibroScan® failed in 16 (11%) patients. The three methods showed similar AUROCs and best cut-off values in transplant and non-transplant patients. In the training set, differences between the AUROCs of ARFI, FibroScan® and ELF to diagnose F $\geqslant$2 (0.879, 0.861, and 0.764, respectively) and cirrhosis (0.936, 0.918, and 0.841) were not statistically significant, although both ultrasound-based methods showed higher accuracy than ELF. The combination of ELF with ARFI or FibroScan® increased the negative and positive predictive values of single tests for the diagnosis of F $\geqslant$2 and cirrhosis. Similar results were obtained when the methods were tested in the validation set.
Conclusions: ARFI is as effective as either FibroScan® or ELF in the non-invasive assessment of liver fibrosis, and its inclusion in an ultrasound device could facilitate its incorporation into routine clinical practice. The combination of ARFI or FibroScan® with ELF may help better identify patients with or without significant fibrosis or cirrhosis.

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Keywords: Acoustic radiation force impulse; Transient elastography; Enhanced liver fibrosis; Liver transplantation.
Received 7 June 2011; received in revised form 1 March 2012; accepted 12 March 2012; available online 17 April 2012

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Abbreviations: LSM, liver stiffness measurement; TE, transient elastography; TIMP-1, tissue inhibitor of matrix metalloproteinase type-1; HA, hyaluronic acid; PIIINP, aminoterminal propeptide of type III procollagen; ELF, enhanced liver fibrosis; ARFI, acoustic radiation force impulse; SWV, shear wave velocity; ROI, region of interest; LT, liver transplantation; BMI, body mass index; kPa, kilopascals; IQR, interquantile range; SD, standard deviation; VC, variation coefficient; AUROC, area under the receiver-operating characteristic curve; Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; LR+, likelihood ratio positive; LR−, likelihood ratio negative; DOR, diagnostic odds ratio.

Introduction

Evaluation of fibrosis is crucial in the assessment of chronic liver disease. Currently, histological assessment based on semi-quantitative scores is considered the best method for evaluating fibrosis, although biopsy has also some drawbacks that have led to the development of techniques geared towards a non-invasive assessment of liver fibrosis [1,2].

Liver stiffness measurement (LSM) using transient elastography (TE, FibroScan®) is accurate in identifying significant fibrosis and especially cirrhosis in several liver diseases including liver transplant recipients [3–7]. Nevertheless, FibroScan® has some limitations, such as LSM failure in patients with narrow intercostal spaces or high body mass index [8] and increased stiffness values in patients with acute hepatitis [9] or extrahepatic cholestasis [10].

Another approach for evaluating liver fibrosis involves the use of serologic markers [2,11–15]. Among them, the Original European Liver Fibrosis panel, that combines tissue inhibitor of matrix metalloproteinase type 1 (TIMP-1), hyaluronic acid (HA), aminoterminal propeptide of type III procollagen (PIIINP), and age, showed good diagnostic accuracy in detecting fibrosis in a large cohort of patients with chronic liver disease [16]. Subsequent studies have evaluated this panel, as well as its simplified modification, ELF (Enhanced Liver Fibrosis), in patients with different liver diseases [16–18]. Not less importantly, ELF has been shown to predict disease progression in several clinical settings [19–21].

Acoustic radiation force impulse (ARFI) is an ultrasound-based technology that uses short-duration, high intensity acoustic pulses to mechanically excite the tissue [22]. These radiation force excitations generate localized tissue displacements that result in shear waves, whose velocity (SWV) of propagation can be assessed in a region of interest (ROI) corresponding to a cylinder, 0.5 cm long and 0.4 cm wide, that can be targeted up to

5.5 cm below the skin. Both the high-energy pulse and the conventional ultrasound pulse are generated by the same ultrasound probe, and results are expressed in m/s. Several studies have analysed the performance of ARFI [22–32], although some of these reports were heterogeneous, with small cohorts of patients and, in some cases, without the inclusion of liver biopsies. Moreover, no study has thus far attempted to combine ARFI with serologic markers in order to improve overall accuracy.

The aim of our study was to prospectively assess ARFI, FibroScan, and ELF and to explore their combined effectiveness in evaluating liver fibrosis, with biopsy serving as the reference standard.

Patients and methods

Patients and study design

One-hundred and seventy-five patients consecutively admitted to our Unit to undergo a liver biopsy in two periods (April 2009–April 2010 and June–November 2011) were prospectively considered for this study. Exclusion criteria included the presence of ascites, chronic kidney failure, and acute or chronic graft rejection in the case of liver transplant (LT) recipients. Only biopsies longer than 15 mm with at least six portal tracts were considered. In addition, we included 10 healthy volunteers who underwent liver stiffness measurement via FibroScan® (Echosens, France) and shear wave velocity measurement with ARFI (Virtual Touch™, ACUSON S2000; Siemens Medical Solutions, USA) on the same day. Our study had been previously approved by the Ethics Committee of Hospital Clinic Barcelona in accordance with the 1975 Declaration of Helsinki. Informed consent was obtained from all patients enrolled in the study. Waist perimeter, as well as height and weight in order to calculate body mass index (BMI), were recorded for all patients.

The design of the study was two-folded: first, we analyzed the performance of the three non-invasive methods and their combinations to assess the presence of liver fibrosis in non-transplant and transplant patients separately. Then, the whole cohort was divided into a training set (patients included between April 2009 and April 2010) and a validation set (patients included in 2011), both sets including transplant and immunocompetent patients.

Liver histology

Biopsies were obtained percutaneously or by transjugular approach, as previously described [33]. Liver specimens were fixed in formalin and embedded in paraffin. Two microns sections were stained with hematoxylin-eosin and Masson's trichrome for histological assessment. A single expert pathologist, blinded to clinical data, examined the samples, and the Scheuer classification was used to estimate the fibrosis stage [34]. Significant fibrosis was defined as $F \geqslant 2$. As stated above, only biopsies >15 mm in length with $\geqslant 6$ portal tracts were analyzed.

ELF panel

The same day of the liver biopsy, 20 ml of blood were obtained in a fasting status. Serum was stored at −80 °C, and PIIINP, HA, and TIMP-1 were measured in all patients by a CE-marked random-access automated clinical immunochemistry analyzer that performs magnetic separation enzyme immunoassay tests (ADVIA Centaur™, Siemens Healthcare Diagnostics, Tarrytown, NY, USA). The ELF score was calculated using the algorithm recommended in the CE-marked assay [ELF = 2.278 + 0.851 ln(HA) + 0.751 ln(PIIINP) + 0.394 ln(TIMP-1)].

Transient elastography

Patients underwent FibroScan® within 15 days of the liver biopsy by a technician who had performed more than 1000 LSMs in patients with chronic liver disease and LT and who was unaware of the result of the biopsy. Liver stiffness was determined on the right lobe of the liver as previously described [6]. The results were expressed in kilopascals (kPa) and the median value of 10 acquisitions was considered for analysis, including only those cases with a success rate higher than 60% and an IQR/result ratio <0.3.

ARFI imaging

Immediately after FibroScan®, the same technician performed a SWV measurement with ARFI imaging. The right lobe of the liver was localized with conventional B-mode ultrasound guidance and ten valid acquisitions were obtained in the ROI placed 2.5 cm below the capsule. All measurements were obtained in the same intercostal space, avoiding large vessels and ribs. The mean, standard deviation (SD), and variation coefficient (SD/mean, VC) of each exploration were recorded for statistical analysis.

Statistical analysis

Quantitative variables are expressed in medians (range) and qualitative variables in (%). Pearson's coefficient was used to evaluate any correlations between FibroScan and ARFI. The relationship between the stages of fibrosis and the non-invasive tests were assessed with a non-parametric test (Kruskal–Wallis analysis). The diagnostic values of ARFI, FibroScan®, and ELF in predicting significant fibrosis and cirrhosis were assessed by calculating the areas under the receiver operator characteristic curve (AUROC). Comparisons of AUROCs were performed according to DeLong method [35]. Best cut-off values were determined by optimization of the Younden index, and sensitivity (Se), specificity (Sp), and positive and negative predictive values (PPV, NPV) were calculated from these same data. Positive and negative likelihood ratios (LR+: Se/(100 – Sp); LR−: (100 − Se)/Sp) were calculated based on the respective sensitivity and specificity values. The diagnostic odds ratio (DOR), which measures the overall accuracy of a diagnostic test [36], was calculated by dividing the LR+ by the LR−. Statistical analyses were performed with SPSS 12.0 (SPSS Inc., Chicago IL), except for AUROC comparisons, which were performed with EPIDAT 3.1.

Results

Patient characteristics

Twenty-nine patients met exclusion criteria, including 20 biopsies shorter than 15 mm or with less than six portal tracts, so the final cohort comprised 146 patients (87 transplant and 59 non-transplant patients). Patients' characteristics are summarized in Table 1.

Applicability and correlation of ARFI and FibroScan® in non-transplant and transplant patients

ARFI imaging was successfully performed in all patients, whereas FibroScan® failed in 16 cases (11%), 8 transplants (9%) and 8 non-transplants (14%). FibroScan® failure was significantly associated with higher BMI and longer abdominal perimeter in the two groups (p <0.02).

ARFI significantly correlated with FibroScan® in non-transplant patients (r = 0.826, p <0.001, Fig. 1A), as well as in transplant recipients (r = 0.887, p <0.001, Fig. 1B).

Relationship between fibrosis staging and non-invasive methods in non-transplant and transplant patients

In non-transplant patients, we found a significant association between fibrosis stages and ARFI, FibroScan®, and ELF (Kruskal–Wallis p <0.001 for all comparisons). Median values of ARFI according to fibrosis stages were 1.17 (F0), 1.4 (F1), 1.46 (F2), 1.77 (F3), and 2.6 m/s (F4), while median FibroScan® measurements were 4.8, 7.5, 8.4, 13.3, and 22.3 kPa, respectively, and median values of ELF panel were 8.7, 8.9, 9.4, 10.6, and 11.

In transplant patients, the relationships between the different non-invasive methods and fibrosis staging were also statistically significant (p <0.001 for all methods). Median ARFI measure-

Table 1. Baseline characteristics of the patients included in the study. Qualitative variables are shown in n (%) and quantitative variables in median (range).

	Non-transplant (n = 59)	Transplant (n = 87)	*p* value
Age (yr)	48 (20-73)	60 (35-76)	0.001
Gender (male)	30 (51)	60 (69)	0.027
Etiology			0.001
HCV	24 (41)	63 (72)	
NASH	8 (14)	2 (2)	
OH	4 (7)	11 (13)	
Cholestatic disease	7 (12)	2 (2)	
HBV	2 (3)	8 (9)	
Others	14 (23)	1 (1)	
BMI (kg/m^2)	25.1 (18.5-44.4)	25.8 (19.3-39.4)	0.32
Abdominal perimeter, cm	90 (65-125)	94 (67-130)	0.1
Transjugular biopsies, number	15 (27)	27 (31)	0.46
Biopsy length, mm	19 (15-40)	20 (15-32)	0.66
Portal tracts, number	9 (6-20)	9 (6-16)	0.89
Time from transplant, mo	n.a.	43 (6-250)	
ALT (IU/ml)	65 (10-768)	62 (9-501)	
Fibrosis stage			
F ≥2	33 (56)	37 (42)	0.1
F4	15 (25)	9 (10)	0.016

HCV, hepatitis C virus; NASH, non-alcoholic steatohepatitits; OH, alcoholic liver disease; HBV, hepatitis B virus; BMI, body mass index; ALT, alanine aminotransferase.

ments according to fibrosis stages were 1.16, 1.29, 1.51, 2.21, and 2.25 m/s; median FibroScan® measurements were 5.2, 7.9, 10, 17.6, and 22.9 kPa; and median ELF values were 8.85, 9.2, 10.5, 11.5, and 13.

In the 10 healthy volunteers, median values for ARFI and FibroScan® were 1.06 m/s and 4.4 kPa, respectively.

Diagnosis of F ⩾2 and cirrhosis in non-transplant and transplant patients

In non-transplant patients, differences between the AUROCs of the three methods for the diagnosis of F ⩾2 were not significantly different (Fig. 2A), while ARFI was significantly better than ELF to diagnose cirrhosis ($p = 0.05$) (Fig. 2B). The diagnostic performance of the three methods is detailed in Table 2.

Fig. 2C and D depict the AUROCs of ARFI, FibroScan®, and ELF for the diagnosis of F ⩾2 and cirrhosis in transplant recipients. Again, while the three methods were comparable to diagnose F ⩾2, ARFI performed significantly better than ELF for cirrhosis ($p = 0.05$). The diagnostic performance of ARFI, FibroScan®, and ELF in transplant patients is shown in Table 2.

Combination of complementary methods in non-transplant and transplant patients

We then aimed at combining the serum marker, ELF, with either ARFI or FibroScan® using the thresholds shown in Table 2. In non-transplant patients, the combination of ARFI and ELF yielded a PPV of 78% and NPV of 85% for the diagnosis of F ⩾2, avoiding

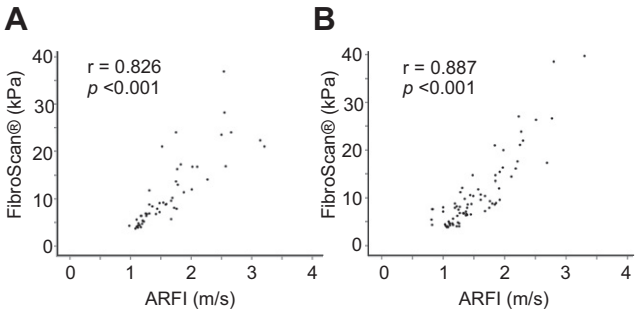

Fig. 1. Correlation between ARFI and FibroScan® in (A) non-transplant and (B) transplant patients.

88% biopsies, and correctly classifying 71% of patients. The combination of FibroScan® and ELF showed a PPV of 85% and NPV of 90%, correctly classifying 59% of patients, and avoiding 68% biopsies. For the diagnosis of cirrhosis, the combination of ELF with ARFI or FibroScan® showed PPV of 93% and 70%, respectively, and NPV of 97% and 97%, respectively. The proportion of correctly classified patients and avoided biopsies was 81% and 85% for the combination of ARFI and ELF and 68% and 74% for the combination of FibroScan® and ELF.

In transplant patients, PPV and NPV of the combination of ARFI and ELF for F ⩾2 were 86% and 88%, avoiding 71% biopsies, and correctly classifying 62% of patients. PPV and NPV of the combination of FibroScan® and ELF were 79% and 87%, avoiding 66% biopsies, and correctly classifying 55% of patients. For the diagnosis of cirrhosis, ARFI and ELF showed PPV and NPV of 50% and 99%, while figures for the combination of FibroScan® and ELF were 46% and 99%, respectively. The proportion of correctly classified patients and avoided biopsies was 71% and 80% for the combination of ARFI and ELF and 62% and 71% for the combination of FibroScan® and ELF.

Diagnosis of F ⩾2 and cirrhosis and combinations of methods in the whole cohort: training and validation sets

As shown in Table 2 and Fig. 2, the three methods exhibited similar cut-off values and high diagnostic accuracy in transplant and non-transplant patients. For this reason, we aimed at simplifying the approach by analysing the entire population with single cut-off values. To this end, the whole cohort was divided into a training set (patients included in 2009–2010, n = 88, 60% of the total population), in which cut-off values were developed, and a validation set (patients included in 2011, n = 58, 40%). Table 3 shows the baseline characteristics of the two groups. Fig. 3A and B depict the AUROCs of the three methods in the training cohort for the diagnosis of F ⩾2 and cirrhosis, respectively; and their diagnostic performance is shown in Table 4. We did not find significant differences between the AUROCs of the three methods for the diagnosis of F ⩾2 or cirrhosis.

When we combined the methods using the cut-offs shown in Table 4 in the training set, the PPV for the tandem use of ELF and ARFI for the diagnosis of F ⩾2 (Fig. 4A) was 89%, while NPV was 82%. The combination correctly classified 54/88 (61%) patients and avoided 63/88 (72%) biopsies. Similarly, the PPV and NPV of the combination of FibroScan® and ELF (Fig. 4B) were 86% and 83% for F ⩾2 in this cohort. Thus, 49/88 patients (56%) were correctly classified avoiding 66% biopsies (58/88).

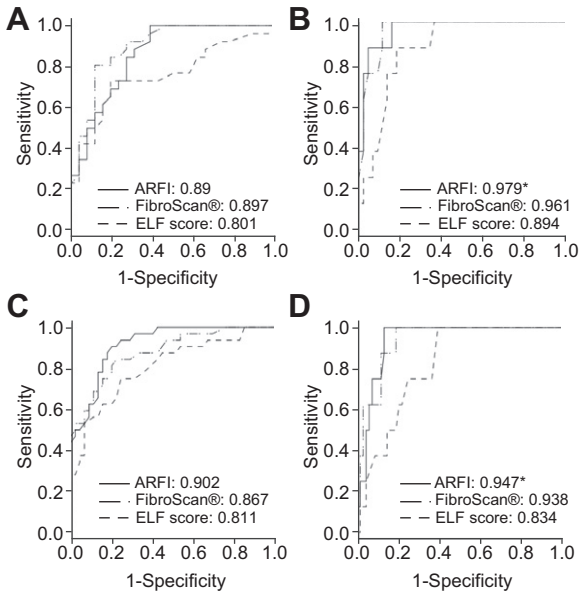

Fig. 2. AUROCs for the diagnosis of F ⩾2 and cirrhosis for ARFI, FibroScan® and ELF, in (A and B) non-transplant and (C and D) transplant patients. *p <0.05 *vs.* ELF.

The combination of ELF and ARFI had a PPV and NPV of 60% and 98% for the presence of cirrhosis, while figures for the combination of FibroScan® and ELF were 54% and 100%, respectively.

AUROCs for the diagnosis of F ⩾2 and cirrhosis in the validation set are shown in Supplementary Fig. 1. The three methods were comparable to diagnose F ⩾2, while ARFI and FibroScan® were significantly better than ELF to diagnose cirrhosis. In the validation set, for the diagnosis of F ⩾2, the combination of ARFI and ELF using the cut-offs developed in the training set had a PPV and NPV of 88% and 95%, respectively, correctly identifying 40/58 patients (69%) and avoiding 44/58 (76%) biopsies. Similarly, the combination of FibroScan® and ELF had a PPV and NPV of 79% and 100%, respectively, correctly classifying 34/58 (59%) patients and avoiding 39/59 (67%) biopsies. For the diagnosis of cirrhosis, PPV and NPV of ARFI plus ELF were 73% and 100%, and figures for

Table 3. Baseline characteristics of the training and validation sets. Qualitative variables are shown in n (%) and quantitative variables in median (range).

	Training (n = 88)	Validation (n = 58)	*p* value
Age, yr	55 (20-75)	59 (20-76)	0.26
Gender (male)	49 (56)	41 (71)	0.07
Etiology			0.48
HCV	55 (62)	32 (55)	
NASH	4 (4)	6 (10)	
OH	8 (9)	7 (12)	
Cholestatic disease	7 (8)	2 (3)	
HBV	7 (8)	3 (5)	
Others	7 (8)	8 (14)	
BMI (kg/m^2)	25.6 (18.5-44.4)	26.5 (20.2-39.6)	0.27
Abdominal perimeter, cm	90 (67-128)	96 (65-130)	0.06
Transjugular biopsies, number	27 (31)	15 (26)	0.53
Biopsy length, mm	19 (15-32)	18 (15-40)	0.72
Portal tracts, number	9 (6-20)	9 (6-16)	0.89
Transplant, %	52 (59)	35 (60)	0.81
ALT (IU/ml)	56 (9-768)	69 (9-501)	
Fibrosis stage			
F ≥2	44 (50)	26 (45)	0.48
F4	13 (15)	11 (19)	0.5

HCV, hepatitis C virus; NASH, non-alcoholic steatohepatitits; OH, alcoholic liver disease; HBV, hepatitis B virus; BMI, body mass index; ALT, alanine aminotransferase.

Table 2. Diagnostic performance of ARFI, FibroScan® and ELF for the diagnosis of F ⩾2 and cirrhosis.

Non-transplant, (n = 59)	Cut-off for F ≥2	Se (%)	Sp (%)	PPV (%)	NPV (%)	LR+	LR-	DOR
ARFI	1.43 m/s	88	73	81	83	3.26	0.16	20.4
FibroScan®	8.25 kPa	85	81	81	84	4.47	0.19	23.5
ELF	9.3	79	77	81	74	3.43	0.27	12.7
	Cut-off for F4							
ARFI	2.05 m/s	93	95	87	98	18.6	0.07	265.7
FibroScan®	16.5 kPa	87	89	59	97	7.91	0.15	54.7
ELF	10.4	93	79	61	97	4.43	0.09	49.2
Transplant, (n = 87)	Cut-off for F ≥2	Se (%)	Sp (%)	PPV (%)	NPV (%)	LR+	LR-	DOR
ARFI	1.39 m/s	89	80	77	91	4.45	0.14	31.8
FibroScan®	8.4 kPa	82	80	76	86	4.1	0.22	18.6
ELF	9.4	86	56	59	85	1.95	0.25	7.8
	Cut-off for F4							
ARFI	1.92 m/s	89	90	50	99	8.9	0.12	74.1
FibroScan®	15.1 kPa	87	89	47	99	7.91	0.15	52.7
ELF	10.3	78	72	24	96	2.78	0.3	9.3

Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; LR+, likelihood ratio positive; LR−, likelihood ratio negative; DOR, diagnostic odds ratio.

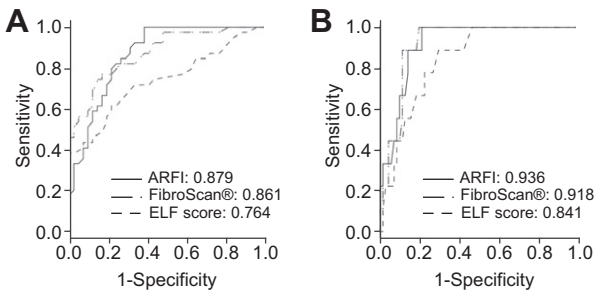

Fig. 3. AUROCs of ARFI, FibroScan® and ELF for the diagnosis of (A) F ⩾2 and (B) cirrhosis in the training set.

the combination of FibroScan® and ELF were 64% and 100%, respectively.

Discussion

In the current prospective study, we have shown that the estimation of shear wave velocity with ARFI can provide a diagnosis of significant fibrosis and cirrhosis as accurate as FibroScan® or ELF, both in transplant recipients and immunocompetent patients with liver disease of varied aetiologies. Not less importantly, the combination of either ARFI or FibroScan® with ELF seems to increase the diagnostic accuracy of single tests, permitting to more confidently discard or confirm the presence of significant fibrosis or cirrhosis.

ARFI software is included in an ultrasound device. Ultrasound guidance is particularly helpful for ensuring that the ROI is placed in such a way that it avoids nearby vessels and ribs. This represents a significant advantage, especially when the region of interest measured by ARFI is smaller than it is for FibroScan®. Consistent with other reports [8], FibroScan® failed in 11% of patients. In contrast, we could measure shear wave velocity with ARFI in all of these same individuals. Most likely, ultrasound guidance helps facilitate the identification of a suitable place for elastographic measurements, thereby resulting in a higher number of patients with valid results. Moreover, ultrasound permits the evaluation of other features such as portal diameter, splenomegaly, and liver surface, which has recently been shown to be highly accurate in the diagnosis of early cirrhosis and seems to provide complementary information to that of liver stiffness [37]. Thus, the ability to perform ARFI and liver surface ultrasound examination during the same procedure offers a significant advantage and may facilitate the early diagnosis of cirrhosis.

Recent studies have suggested that the combination of serum markers with FibroScan® is highly accurate in the identification of liver fibrosis [38,39]. In our population, the combined use of ELF with either FibroScan® or ARFI increased the PPV and NPV of single tests, still offering reliable identification of significant fibrosis and cirrhosis in a large proportion of patients. An important number of patients could thus have avoided liver biopsy, and had their disease staged with a high level of confidence. While this approach seems logical, as it uses "complementary" methods, our results are based on a relatively low number of patients, thus larger, multicenter studies should be encouraged to confirm our findings.

It is important to acknowledge that the heterogeneous nature of the cohort is a significant limitation of our study, which included both transplant and non-transplant patients with liver disease of varied aetiologies. The combination of transplant and non-transplant patients in the same group may be particularly difficult to interpret, as fibrosis deposition and staging may be different in these groups of patients, and indeed a large number of transplant patients in our cohort did not have significant fibrosis. To try to solve in part this drawback, we first studied separately transplant and non-transplant patients, being able to show similar results in terms of diagnostic accuracy and best cut-off values in the two groups. This allowed us to analyze the entire cohort splitting the whole population into a training set and a validation set, which were comparable in terms of transplant patients proportion and prevalence of significant fibrosis and cirrhosis. Regarding the different aetiologies of the liver diseases, although our findings would anyway require further confirmation in single-etiology studies, it should be kept in mind that daily clinical work includes patients with liver disease of different aetiologies, and perhaps the results of the current study are more representative of what is typically seen in routine clinical practice.

In summary, ARFI, FibroScan® and ELF are reliable methods for assessing fibrosis in patients with varying forms of liver disease, including liver transplant recipients. Indeed, the combined use of ELF with either ARFI or FibroScan® seems a promising approach that may increase the diagnostic accuracy of these tests. The incorporation of ARFI in conventional ultrasound devices may facilitate the introduction of elastography into surveillance programs.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Table 4. Diagnostic performance of ARFI, FibroScan® and ELF for the diagnosis of F ⩾2 and cirrhosis in the training set (n = 88).

	Cut-off for F ≥2	Se (%)	Sp (%)	PPV (%)	NPV (%)	LR+	LR-	DOR
ARFI	1.44 m/s	85	76	77	82	3.54	0.19	18.6
FibroScan®	8.3 kPa	77	83	81	79	4.53	0.28	16.2
ELF	9.4	75	68	70	73	2.32	0.37	6.3
	Cut-off for F4							
ARFI	1.9 m/s	92	87	54	98	7.07	0.09	78.5
FibroScan®	14.8 kPa	89	84	40	98	5.56	0.13	42.7
ELF	10.3	92	72	36	98	3.28	0.11	29.8

Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; LR+, likelihood ratio positive; LR−, likelihood ratio negative; DOR, diagnostic odds ratio.

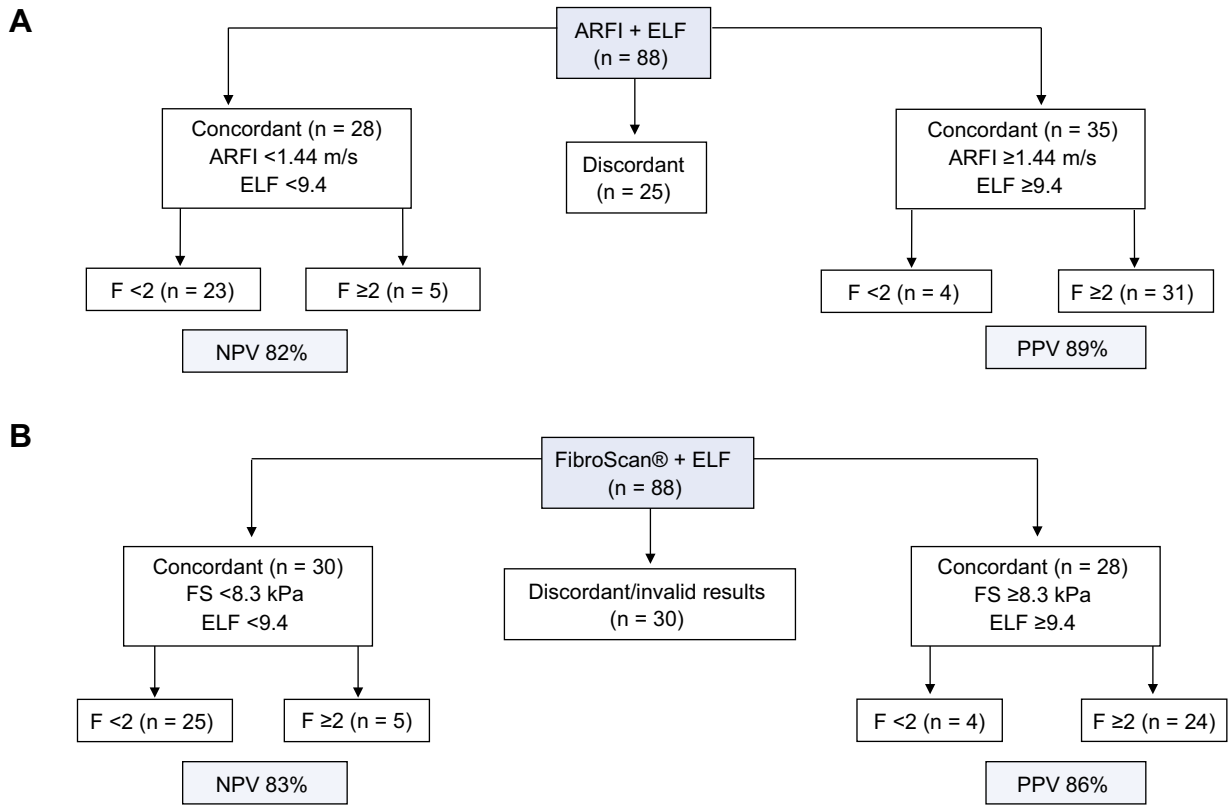

Fig. 4. Flowchart of the synchronous application of ELF with either (A) ARFI or (B) FibroScan® for the diagnosis of F ⩾2 in the training set.

Financial support

G. Crespo is supported by Grants from Hospital Clínic (Ajut a la Recerca Josep Font) and the Fundación BBVA, and Z. Mariño by the Fundación BBVA and CIBERehd. Dr. W. Jiménez has received research funding from the Dirección General de Investigación Científica y Técnica (SAF-08839) and from the Agència de Gestió d'Ajuts Universitaris i de Recerca (SGR 2009/1496). Dr. Navasa received support, in part, from the Instituto de Salud Carlos III (PI 10/01551), co-funded by the European Regional Development Fund (ERDF). CIBERehd is funded by the Instituto de Salud Carlos III, the Ministerio de Ciencia e Innovación, Spain. The authors thank Siemens Healthcare Diagnostics (Tarrytown, NY, USA) for generously supplying the reagents to measure the fibrosis markers.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jhep.2012.03.016.

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