Performance of Acoustic Radiation Force Impulse Imaging in Staging Liver Fibrosis and Cirrhosis in Comparison to Serum Fibrosis Markers in Patients with NAFLD

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Abstract

Background: ARFI elastography proved to have excellent performance diagnosing liver cirrhosis and significant fibrosis in viral hepatitis. This study evaluated the diagnostic accuracy of ARFI elastography in different liver segments in overweight and obese patients with non-alcoholic fatty liver disease (NAFLD) and steatohepatitis (NASH).

Methods: A total of 89 patients with NAFLD with BMI >24kg/m² underwent liver biopsy and liver stiffness (LS) measurement by ARFI elastography in segments 8 and 6.

Results: Comparing LS in segment 8 and 6, 10 valid measurements were successful in segment 8 while 5% failure in segment 6. The diagnostic performance of segment 8 and 6 for >!F3 and F4 were 0.99, 0.99, 0.98 and 0.98, respectively. A significant correlation was detected between LS in segment 8 and 6 with the stages of liver fibrosis ($p<0.001$ and $p<0.001$, respectively) as well as with NAFLD fibrosis score, FIB-4 and APRI ($p=0.004$, $p=0.041$, $p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$). The discordance between liver biopsy and LS in segment 8 was 5 (6%) and in segment 6 was 4 (5%) and was prominent in (F0-F2). No significant discordance between both segments for the different stages of liver fibrosis. No significant correlation and no significant difference were observed between LS in both segments and the different grades of steatosis or NASH.

Conclusions: Liver stiffness (LS) by ARFI elastography is equally successful in several segments of the liver in obese and overweight patients with NAFLD and NASH. An excellent performance was detected for liver cirrhosis and advanced fibrosis and was equally found in the different liver segments in this group of patients.

Key Words: Acoustic Radiation Force Impulse (ARFI) – Non-alcoholic fatty liver disease (NAFLD) – Liver fibrosis and cirrhosis.

Introduction

THE new era of anti-HCV treatment lead to its cure and eradication. Moreover, the immunological protection against HBV reduced its prevalence worldwide. The non-alcoholic steatohepatitis is currently the most common cause of liver disease in the western world [1] and is a worldwide progressing epidemiological health problem [2]. The rise of NAFLD prevalence is in line with the increase of obesity and type 2 diabetes [3] and robustly increases in morbidly obese adults [4] as well as in children [5]. The spectrum of NAFLD is wide, ranging from the benign simple steatosis to steatohepatitis (NASH) with its consequences namely liver fibrosis, cirrhosis and even hepatocellular carcinoma [6]. The pathophysiology associated with the progress of simple steatosis to steatohepatitis is complex, multifactorial and associated with a genetic predisposition [7]. Liver related mortality follows the development of NASH and the advanced stages of fibrosis [8]. Thus, patients’ stratification into simple steatosis and NASH is crucial for prognosis, monitoring and screening programs. Liver biopsy is until now the gold standard classifying this group of patients. Kleiner’s “NAS score” distinguishes probable or definite NASH ≥5 from <3 absence of NASH [9]. However, liver biopsy is associated with several disadvantages including costs, invasiveness inter and intra-observer variability [10] as well as complications and related mortality [11,12]. Therefore, several non-invasive tests were developed to replace liver biopsy; BARD score [13], FIB-4 [14], NAFLD fibrosis score [15], ELF test [16] and Fibrotest/
Fibromax [17] with the NAFLD fibrosis score and FIB-4 showed the best performances [18].

The ultrasound imaging is the most commonly used method diagnosing NAFLD in the form of hyperechogenic liver. However, the sensitivity is only 60% and decreases in morbidly obese patients [19,20]. Nevertheless, there is no accurate assessment of the stage of fibrosis. The transient elastography (TE) showed excellent performance staging liver fibrosis in patients with viral hepatitis [21]. The use of TE in staging fibrosis in patients with NAFLD using the M probe was associated with 10.2% failure rate in obese patients [22]. The subcutaneous fat in those patients hampers the spread of the shear wave and overestimates of liver stiffness (LS) and its corresponding stage of fibrosis [23]. The introduction of XL probe reduced the failure rate; however, this implicated the need of sonographic assessment of the subcutaneous fat before measurement >25mm. Moreover the cut off values are lower than those of M probe and new adjusted cut off values are required [24].

ARFI elastography is an ultrasound imaging technique with the same shear wave concept of TE with the advantage of being included in the ultrasound machine. Several meta-analyses showed that LS measured by ARFI elastography showed diagnostic accuracy equal to that of TE diagnosing liver cirrhosis and significant fibrosis in viral hepatitis [25,26]. Moreover, studies showed that ARFI measurement is not influenced by the subcutaneous fat [27]. Staging of liver fibrosis in patients with NAFLD/NASH is not thoroughly evaluated. Therefore, the aim of this study was to assess the influence of NAFLD/NASH on liver fibrosis staging by ARFI elastography and its diagnostic performance.

Patients and Methods

The study was performed in compliance with the declaration of Helsinki and approval of the local Ethical Committee. Written informed consent was obtained from all patients.

A total of 89 patients with BMI >24kg/m², referred to the ultrasound unit of the Department of Gastroenterology, Hepatology and Endocrinology of Hannover Medical School were consecutively enrolled in this prospective study from Feb. 2012 – June 2013. All patients received abdominal ultrasound examination including ARFI elastography on the same day and liver biopsy. All patients with sonographical diagnosed NAFLD, elevated transaminases <2 folds and BMI >24kg/m² were subjected to liver biopsy and were included in this study. Exclusion criteria were: BMI <24kg/m², refusal to undergo liver biopsy, non-feasibility of LS measurements by ARFI in both liver segments, known malignancy and terminal liver diseases. Women with >20g alcohol/week and men >20g alcohol/week were excluded from the study. Patients with concomitant liver diseases as HBV, HCV, autoimmune liver diseases and other liver etiologies were excluded from the study.

Liver histology:

Percutaneous liver biopsy was performed using the 16G Menghini needle under ultrasound guidance. Liver biopsy specimens were fixed on formalin and embedded in paraffin and stained with hematoxylin-eosin and Masson trichrome stains. Liver histology was assessed by an experienced pathologists blinded to the clinical, laboratory and stiffness data. NAFLD was diagnosed with at least 5% macrovesicular steatosis. Specimens shorter than 10mm and 6 portal tracts were discarded. Histological classification was performed according to Kleiner et al., classification score [9]. Steatosis grade: 0=steatosis <5%, 1=steatosis 5-33%, 2=steatosis >33-66%, 3=steatosis >66%. Hepatic inflammation was graded according to the NAFLD Activity Score (NAS) (from 0-8): The sum of steatosis (from 0-3), lobular inflammation (0-3) and ballooning (0-2), activity score >5 was classified as NASH [9]. The Stage of fibrosis from 0-4 was classified according to Kleiner et al., in patients with NAFLD [9].

Laboratory parameters:

Serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma glutamyl transferase (γ-GT), bilirubin, glucose, cholesterol, cholesterol LDL, triglycerides, platelets count and albumin were recorded after an overnight fast.

Laboratory markers of liver fibrosis:

Aspartate aminotransferase (AST)/platelet ratio index; APRI: AST/platelet count (x10³/l) x 100 [29] FIB-4: Age x AST (U/l)/platelet count (x10⁹/l) x q alanine aminotransferase (ALT, U/l) [18], NAFLD fibrosis score: −1.675+0.037 x age (years) +0.094 x BMI (kg/m²) +1.13 x impaired fasting glycaemia/diabetes (yes=1, No=0) +0.99 x AST/ALT ratio −0.013 x platelet count (x10⁹/l) −0.66 x albumin (g/dl) [15].

Abdominal ultrasonography:

Ultrasonographic examination of the liver were carried out by a DEGUM II-III certified physician (www.degum.de) routinely in all patients using
the C4-1 array (Siemens Acuson S2000, Munich, Germany).

**ARFI elastography:**

ARFI is integrated in a conventional ultrasonographic system (Siemens ACUSON S2000 Virtual Touch™ Tissue Quantification; Siemens, Munich, Germany) with a standard band broad 4-1 MHz curved array. This allows the placement of the “Region of Interest” (ROI size: C4-1, 10mmx6mm) under sight in ultrasonographic B-mode. The principles of ARFI elastography is described in details in Nightingale et al., [30] and in the current EFSUMB guidelines [31]. The principle depends on inducing mechanical tissue excitation by the short-duration acoustic pulses with a fixed frequency (2.67 MHz) at the ROI with consequent localized displacement in the tissue. The tissue’s displacement results in propagation of the shear wave away from the region of excitation which is collected through an ultrasonic correlation-based method. The speed of the shear wave of the tissue is the time to the maximum laterally displaced collected ultrasound beam and is expressed in meters per second (m/s). Measurements were made at same day before liver biopsy. Measurements were taken while patients were lying in the dorsal decubitus, in segment 8 and 6 with an intercostal approach with the right arm maximally abducted. Care was taken to minimize the pressure exerted with the transducer. During examinations, we avoided placement of ROI on blood vessels, biliary radicles as well as focal lesions. In all patients, ARFI elastography was performed with an insertion of at least 1-2cm below the liver capsule to achieve the highest diagnostic accuracy [32].

**Statistical analysis:**

SPSS software was used for statistical analysis (version 18.0, SPSS, Chicago, USA). All data are presented as mean ± standard deviation (SD). p-values less than 0.05 were considered statistically significant. Continuous data were expressed as median or mean and standard deviation (SD). The statistical significance of intergroup differences, categorical variables were compared by means of Mann-Whitney U-test or Kruskal-Wallis. Comparisons between liver stiffness in segment 8 and segment 6 at the different stages of liver fibrosis, grade of steatosis as well as NASH was done using Wilcoxon Mann-Whitney paired t-test. Correlations between parameters were expressed with Spearman’s two-tailed pairwise correlation coefficients, as appropriate. The uni-and multivariate regression analysis was used to detect the associations between the variables with determining the correlations coefficient. The overall diagnostic performance of ARFI as well as the other fibrosis markers was assessed using the receiver-operating characteristics curves. Sensitivity, specificity, positive and negative predictive values (PPV and NPV), positive and negative likelihood ratio (PLR and NLR) and 95% confidence intervals were calculated. Cut off points of NAFLD fibrosis score, FIB-4 and APRI for F3 and F4 model were derived from the literature.

**Results**

A total of 89 patients with NAFLD were enrolled in this study (mean age 51 ± 12; 52% male). The patients’ characteristics are illustrated in Table (1). LS by ARFI was successful in all patients in segment 8 and failed in 4 patients in segment 6. Serum AST and ALT were below 2 folds above the ULN. Mean γ-GT was 3 folds above the ULN and mean total cholesterol was slightly elevated. All the other laboratory parameters were in the normal range. The mean BMI of the study cohort 31 ± 6kg/m², morbidly obese 7 (8%), 37 (42%) had steatosis grade 3 (>66%) and 47 (53%) had NASH.

**Liver stiffness by ARFI elastography:**

The mean LS by ARFI in Seg 8 and Seg 6 were 1.36±0.63m/s and 1.39±0.63m/s. The mean LS measured by ARFI in Seg 8 and Seg 6 increased gradually with corresponding rise of liver fibrosis stages (Seg 8: <F2–≥F2 p=0.009, ≥F2–≥F3 p<0.001, ≥F3–F4 p=0.001) and (Seg 6< F2–≥F2 p=0.031, ≥F2–≥F3 p<0.001, ≥F3–F4 p<0.001). Fig. (1) illustrates the simultaneous rise of LS by ARFI in accordance to the stages of liver fibrosis.

<table>
<thead>
<tr>
<th>Stage</th>
<th>LS Seg 8</th>
<th>LS Seg 6</th>
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<tbody>
<tr>
<td>S0</td>
<td>1.1±0.63</td>
<td>1.1±0.63</td>
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<tr>
<td>S1</td>
<td>1.3±0.63</td>
<td>1.4±0.63</td>
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<tr>
<td>S2</td>
<td>1.5±0.63</td>
<td>1.5±0.63</td>
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<tr>
<td>S3</td>
<td>1.6±0.63</td>
<td>1.7±0.63</td>
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<tr>
<td>S4</td>
<td>1.8±0.63</td>
<td>1.9±0.63</td>
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</table>

*Note: LS: Liver stiffness, ULN: Upper limit of normal.*

**ARFI elastography in relation to NAFLD & NASH:**

There was no significant difference as regards LS Seg 8 and Seg 6 on one hand and NASH on the other hand (LS Seg 8: 1.35±0.61 vs 1.38±0.65m/s, p=0.818; LS Seg 6: 1.33±0.63 vs 1.44±0.63m/s, p=0.439). Similarly, LS measured by ARFI didn’t show a significant difference in accordance to the increase of the grade of steatosis (S0 vs S1; LS Seg 8: 1.1±0.2 vs 1.39±0.62m/s, p=0.568; LS Seg 6: 1.1±0.1 vs 1.45±0.63m/s, p=0.401), (S1 vs S2; LS Seg 8: 1.39±0.62 vs 1.39±0.66, p=0.83; LS Seg 6: 1.45±0.63 vs 1.35±0.56, p=0.47), (S2 vs S3; LS Seg 8: 1.39±0.66 vs 1.35±0.67, p=0.698; LS Seg 6: 1.35±0.56 vs 1.39±0.69; p=0.846).
Table (1): Baseline characteristics of the study cohort.

<table>
<thead>
<tr>
<th>Study cohort N=89</th>
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<tr>
<td>Age</td>
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<tr>
<td>Male gender</td>
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<tr>
<td>Diabetes</td>
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<tr>
<td>Body mass index mean ±SD</td>
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<td>&lt;25</td>
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<td>25-30</td>
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<tr>
<td>30-40</td>
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<tr>
<td>≥40</td>
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</table>

**Laboratory parameters:**

| ALT | IU/L | 70±57 |
| AST | IU/L | 57±61 |
| GGT | IU/L | 259±600 |
| Alkaline phosphatase | IU/L | 98±50 |
| Bilirubin | μmol/L | 17±40 |
| Albumin | g/dl | 3.9±4 |
| Platelets | x 10⁹/L | 215±71 |
| Total cholesterol | mmol/L | 205±41 |
| LDL cholesterol | mmol/L | 119±60 |
| Triglycerides | mmol/L | 133±296 |
| Glucose | mmol/L | 2.5±3.4 |

**Liver histology:**

| Fibrosis | 0/1/2/3/4 | 29 (30)/22 (25)/18 (21)/7 (8)/15 (17) |
| Steatosis grade | SO/S1/S2/S3 nb(%) | 4 (5)/31 (35)/16 (18)/37 (42) |
| NAS | ≤4/>4 | 41 (47)/47 (53) |

**Liver stiffness:**

| Mean arfi seg 8 | m/s | 1.36±0.63 |
| Mean arfi seg 6 | m/s | 1.39±0.63 |

**Median IQR/liver stiffness:**

| Arfi seg 8 | 0.19 |
| Arfi seg 6 | 0.17 |

**Success rate:**

| Arfi seg 8 | 100% |
| Arfi seg 6 | 95% |

**Abbreviations:**

- NAFLD: Non-alcoholic fatty liver disease.
- SD: Standard deviation.
- nb: Number.
- ALT: Alanine transaminase.
- AST: Aspartate transaminase.
- GGT: Gamma glutamyltransferase.
- IU/L: International unit per liter.
- μmol/L: Micromole per liter.
- mmol/L: Mill mole per liter.
- g/dl: Gram per deciliter.
- m/s: Meter per second.
- NAS, NAFLD: Activity score.
- Seg: Segment.

On the other hand, comparing LS measured in Seg 8 vs Seg 6; LS in Seg 8 was significantly lower in patients with NASH than in Seg 6 (1.34±0.65m/s vs 1.44±0.63m/s, p=0.008). Similarly, LS was lower in Seg 8 than Seg 6 in obese patients with BMI (30-39kg/m²) (1.17±0.50m/s vs 1.23±0.53m/s, p=0.042). However, there was no significant difference in LS in the morbidly obese patients (BMI >40kg/m²) p=0.405, overweight patients (BMI: >25-29kg/m²) p=0.042 and those with (BMI 25kg/m²) p=0.199. There was also no difference in the LS between both segments as regards the different grades of steatosis (S 1: p=0.107, S2: p=0.245, S3: p=0.116).

Although the liver fibrosis correlated positively with the grade of liver steatosis (r=0.252, p=0.018) and NASH (r=0.296, p=0.005), there was no significant correlations between LS Seg 8 and Seg 6 and liver steatosis or NASH (Seg 8 and steatosis: r=0.056, p=0.601; Seg 8 and (NAFLD activity score (NAS): r=−0.047, p=0.663) and (Seg 6 and steatosis: r=0.181, p=0.091; Seg 6 and NAFLD activity Score (NAS): r=0.135, p=0.211). However, a weak significant correlation was observed between LS in Seg 6 and BMI (r=0.245, p=0.021), but no correlation was detected between LS in Seg 8 and BMI.

In the univariate analysis, where the stage of fibrosis is the dependent factor, LS Seg 8 and Seg 6 were the independent factors predicting liver fibrosis (r=0.816, p<0.006; r=0.801, p<0.001). In the multivariate analysis where the stage of fibrosis is the dependent factor and other independent factors were added (BMI, age, gender, NASH, grade of steatosis, DM, cholesterol and TG), LS in Seg 8, LS in Seg 6 NASH and DM were the
independent factors predicting the stage of fibrosis ($\beta=1.896, p<0.001; \beta=1.998, p<0.001; \beta=0.779, p=0.004$ and $\beta=0.661, p=0.006$, respectively).

**ARFI elastography and serum fibrosis markers:**

A highly significant correlation was also detected between LS Seg 8 and Seg 6 ($r=0.862, p<0.001$). A positive significant correlation was similarly detected between LS Seg 8 and Seg 6 and NAFLD fibrosis-score ($r=0.544, p<0.001$, $r=0.544, p<0.001$), FIB-4 ($r=0.587, p<0.001$; $r=0.569, p<0.001$), APRI ($r=0.610, p<0.001$; $r=0.581, p<0.001$) (Fig. 2).

**Diagnostic performance of ARFI elastography predicting the different stages of liver fibrosis:**

LS in Seg 8 and in Seg 6 can diagnose liver cirrhosis (F4) at cut off (1.99 and 1.95 m/s, respectively) with AUC (0.98 and 0.98) and F3 at cut off (1.53 and 1.55 m/s, respectively) with AUC (0.99 and 0.99) and F2 at cut off (1.19 and 1.18 m/s, respectively) with AUC (0.89 and 0.88) (Fig. 3).

The diagnostic performance of other laboratory parameters predicting liver cirrhosis were (NAFLD fibrosis score: Cut off: 1.57 at AUC 0.93; FIB-4: Cut off: 2.75 at AUC 0.79; APRI: Cut off: 1.67 at AUC: 0.70; AST/ALT: Cut off: 1.18 at AUC: 0.72) (Fig. 4).

**Failure rate and discordance of LS by ARFI:**

All measurements were successful in Segment 8, while in segment 6, LS measurement failed in 4 patients with 5% failure rate; the grade S3 (>66%) in 2 patients, S2 (>33%) in one patient and S1 (>5%) in one patient. NASH was only detected in one patient and the stage fibrosis varied between (F0-F1) with a mean BMI 30 kg/m$^2$.

There was no significant difference or discordance was detected between LS measured in Seg 6 and Seg 8 at the different stages of liver fibrosis (F<2, $p=0.335$; F≥2, $p=0.631$; F≥3, $p=0.605$; F=4, $p=0.759$).

In 4 patients, discordance was detected between the LS measured in Seg 8 and Seg 6 on one hand and liver biopsy on the other hand. All 4 patients showed overestimation of LS in comparison to the stage of fibrosis F2 for F0. Three of them are having grade (S2-S3), NASH (NAS>4), BMI ranged from (26-38) kg/m$^2$ and 3 females and one male. LS measured in Seg 8 was also overestimated (F3) for (F0) in a female patient with BMI 33.3 kg/m$^2$, S2 steatosis and NAS >4. A biopsy error (confirmed by APRI and the LS measured in Seg 8 and Seg 6) was diagnosed in one patient; where the 3 measurements showed liver cirrhosis and liver biopsy showed F2 with S 1 no NASH and BMI >32 kg/m$^2$.

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**Fig. (1):** Box plot analysis showing the relationship of liver stiffness (LS) measured using ARFI (A) in segment 8, (B) in segment 6 and the stages of liver fibrosis in overweight and obese patients with NAFLD/NASH. A significant difference was detected between the different stages of liver fibrosis and LS in segment 8 and 6.

**Abbreviations:** Seg: Segment. m/s: Meter per second. $p$-value <0.05 was considered significant.
**Fig. (2):** Correlation between liver stiffness values in segment 8 and in segment 6 and (A) NAFLD fibrosis score and (B) FIB-4 score. A significant positive correlation was detected between NAFLD fibrosis score, FIB-4 score and LS in segment 8 and segment 6.

**Abbreviations:** LS: Liver stiffness. Seg: Segment. m/s: Meter per second.

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**Stage of fibrosis**

<table>
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<tr>
<th></th>
<th>AUROC 95% CI</th>
<th>Cut off</th>
<th>Sn (%)</th>
<th>Sp (%)</th>
<th>PPV</th>
<th>NPV</th>
<th>LR+</th>
<th>LR-</th>
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<td><strong>F4</strong></td>
<td>ARFI Seg 8</td>
<td>0.98 (95-100)</td>
<td>1.99</td>
<td>86</td>
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<td>86</td>
<td>96</td>
<td>21</td>
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<tr>
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<td>ARFI Seg 6</td>
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<td>99</td>
<td>95</td>
<td>96</td>
<td>61</td>
</tr>
<tr>
<td><strong>F3</strong></td>
<td>ARFI Seg 8</td>
<td>0.99 (98-100)</td>
<td>1.53</td>
<td>96</td>
<td>100</td>
<td>100</td>
<td>98</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>ARFI Seg 6</td>
<td>0.99 (99-100)</td>
<td>1.55</td>
<td>96</td>
<td>100</td>
<td>100</td>
<td>98</td>
<td>–</td>
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<tr>
<td><strong>F2</strong></td>
<td>ARFI Seg 8</td>
<td>0.89 (82-96)</td>
<td>1.19</td>
<td>81</td>
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<td>89</td>
<td>82</td>
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<td></td>
<td>ARFI Seg 6</td>
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<td>84</td>
<td>90</td>
<td>86</td>
<td>85</td>
<td>8.57</td>
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</table>

**Fig. (3):** ROC curves showing the diagnostic performance of LS using ARFI Elastography in segment 8 and in segment 6 for predicting (A) liver cirrhosis and (B) advanced fibrosis in overweight and obese patients with NAFLD/NASH. The liver stiffness in both segments showed high and almost similar performance for liver cirrhosis and advanced fibrosis (0.98, 0.98, 0.99, and 0.99, respectively).

Liver cirrhosis 

<table>
<thead>
<tr>
<th></th>
<th>AUROC 95% CI</th>
<th>Cut off</th>
<th>Sn (%)</th>
<th>Sp (%)</th>
<th>PPV</th>
<th>NPV</th>
<th>LR+</th>
<th>LR-</th>
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<tr>
<td>NAFLD fibrosis score</td>
<td>0.93 (83-100)</td>
<td>1.57</td>
<td>77</td>
<td>85</td>
<td>48</td>
<td>95</td>
<td>5.03</td>
<td>0.27</td>
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<tr>
<td>FIB-4</td>
<td>0.79 (56-100)</td>
<td>2.75</td>
<td>74</td>
<td>91</td>
<td>57</td>
<td>95</td>
<td>8</td>
<td>0.30</td>
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<tr>
<td>APRI</td>
<td>0.70 (34-100)</td>
<td>1.67</td>
<td>73</td>
<td>92</td>
<td>62</td>
<td>95</td>
<td>9.45</td>
<td>0.30</td>
</tr>
</tbody>
</table>

Fig. (4): ROC curves showing the diagnostic performance of LS using ARFI Elastography in segment 8 and segment 6 and the different non-invasive scoring systems for predicting (A) liver cirrhosis and (B) advanced fibrosis in overweight patients with NAFLD. The liver stiffness using ARFI elastography in segment 8 and segment 6 showed the best performance for liver cirrhosis and advanced fibrosis (0.98, 0.98, 0.99, and 0.99, respectively).


Discussion

The steady rise of the prevalence of NAFLD with consequent development of NASH and progression to fibrosis increased the demand of a non-invasive, safe and easy method, that can regularly staging liver fibrosis and predicting its prognosis. LS measurement by ARFI elastography is influenced by several extrinsic factors [32-34]. In this study we evaluated the performance of LS by ARFI at different region of interest in two different segments in comparison to liver biopsy in patients with NAFLD and NASH in the overweight and obese patients.

In the present study, LS by ARFI elastography confirmed the comparable feasibility of LS measurement in several segments in this group of patients. Moreover, it illustrated the excellent performance diagnosing liver cirrhosis and advanced fibrosis (>F3) and good performance diagnosing significant fibrosis (>F2).

This study also emphasized that LS measurement by ARFI elastography was not influenced by the different grades of liver steatosis or the presence of NASH in this patients’ group. These findings were confirmed in both segments. Although, there was no difference in the LS measured between both segments at different grades of steatosis, the mean LS in segment 6 was higher in patients with NASH. This also confirms that LS by ARFI is not influenced by the presence of steatosis or NASH in segment 8.

In the present study, we also showed that LS by ARFI was not influenced by BMI. All patients had BMI >24kg/m² with the range of overweight, obese and 8% in morbidly obese. One finding is that LS in segment 6 correlated with BMI and a similar borderline difference was detected between LS in segment 8 and segment 6 in obese patients. However, this weak correlation and this borderline difference were not influencing factors in the multivariate analysis, affecting the staging of liver fibrosis. This is completely different for the TE where LS measured by the M probe is limited by BMI >30kg/m² and skin capsular distance >25mm [24,25] and LS measured by the XL probe in morbidly obese patients (BMI >40kg/m²) [24].
The diagnostic accuracies of both segments diagnosing the different stages of liver fibrosis were almost similar. Moreover, the values in segment 8 were relatively lower than those in segment 6, however, the difference did not influence the stage of liver fibrosis. It is also worth noting that LS in segment 6 showed higher values in patients with NASH than those in segment 8, but again this did not change the stage of liver fibrosis.

In our study, the applied quality criteria were similar to those of transient elastography; 10 successful measurements with more than 60% success rate and an interquartile range of less than 30% of the mean value for both segments. There was no failure rate in segment 8 while segment 6 showed 5% failure rate in 4 patients. In those four patients, the common factors were the mean BMI was 30kg/m² and the lower stages of liver fibrosis was (F0-F1). Which could be explained by lower performance (although good) in the lower stages of liver fibrosis was influenced by the higher BMI in relatively deep seated liver segment 6 and lead to failure of measurement.

The discordance between the LB and both segments was detected in the lower fibrosis stages (F0-F2), higher BMI and all patients had NASH with an overestimation of stage of fibrosis (F0-F2 to F3-F4). The discordance was also detected in segment 8 in one patient with F3. However, no discordance was observed for F0. This finding also showed that in the lower stages of liver fibrosis, high BMI and the presence of NASH the diagnostic performance is reduced. This overestimation was also reported by TE [24] and other studies with ARFI elastography [25].

It is worth noting that there was no discordance in the measurement between both segments in LS at the different stages of liver fibrosis. This is not in line with the previously published study by Friedrich-rust and colleagues which showed that a difference of one fibrosis stage between the right and the left is present [25]. However, the left lobe due to its position and the presence of hepatic segment of inferior vena cava results in increase of the liver stiffness. This theory is not applied on segment 6.

Liver stiffness by ARFI elastography showed also a significantly high correlation with histological liver fibrosis which is not in line with Friedrich-Rust study [25]. Moreover, a significant correlation was also detected with the NAFLD fibrosis score, FIB-4 as well as APRI score. Interestingly, ARFI showed a higher diagnostic performance than the previously mentioned tests for the different stages of liver fibrosis in patients with NAFLD.

This study also showed that the proposed cut off values by ARFI elastography for patients with NASH and NAFLD were higher than those described for viral hepatitis [25,26]. This is also in line with the other published studies [27,34-36]. This study also showed that LS by ARFI elastography was able to discriminate patients with and without NASH only in Seg 6 which was also reported by Palmeri’s study [27].

In conclusion, LS measurement by ARFI elastography has several advantages; being included in the ultrasound machine allowing the quantitative confirmation of the qualitative assessment of NAFLD disease on liver fibrosis stages. Moreover, ARFI elastography is a non-invasive method that requires 5 minutes during the bedside ultrasonographic examination with the mobile region of interest “ROI” and allows the evaluation of the different segments of liver under vision avoiding all the other influencing factors. LS measured by ARFI elastography is not influenced by NAFLD, NASH or BMI and does not require a special probe for measurement. LS measurement is feasible and accurate in segment 8 and segment 6 with excellent diagnostic accuracy for diagnosing liver cirrhosis and significant fibrosis. Specific cut off values are recommended for patients with NAFLD/NASH.

References


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