Evaluation of Acoustic Radiation Force Impulse (ARFI) for Fibrosis Staging in Chronic Liver Diseases

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ABSTRAK

Latar belakang: *acoustic radiation force impulse (ARFI) merupakan metode non invasif baru untuk penilaian derajat fibrosis hati. Dengan adanya integrasi ultrasonografi mode B, ARFI dapat digunakan untuk menilai kondisi jaringan hati. Meskipun demikian, kemampuan diagnostik ARFI saat ini masih terus dievaluasi. Terlebih lagi, belum tersedia data mengenai penggunaan ARFI pada populasi kami. Penelitian ini bertujuan mengevaluasi kemampuan diagnostik ARFI sebagai alternatif modalitas penilaian derajat fibrosis secara non invasif pada pasien hepatitis B dan hepatitis C kronik pada populasi kami.* ***Metode:*** *dilakukan penelitian potong lintang untuk membandingkan gambaran ARFI dan elastografi transien pada pasien yang diperiksakan biopsi hepar di Rumah Sakit Cipto Mangunkusumo. Derajat fibrosis menggunakan sistem skor METAVIR sebagai acuan baku. Sebanyak 43 pasien diikutsertakan dalam penelitian ini. Nilai cut-off ditentukan berdasarkan kurva receiver-operating characteristic (ROC).* ***Hasil:*** *derajat kekakuan hati melalui pemeriksaan ARFI maupun transien elastografi (TE) berkorelasi sedang dengan skor METAVIR dengan skor masing-masing 0,581 dan 0,613 ($p<0,01$). Akurasi diagnostik ARFI untuk memprediksi fibrosis signifikan ($F\geq2$) memiliki area under receiver operating characteristic curve (AUROC) 0,773 (IK 95% 0,616-0,930) dan bahkan jauh lebih baik untuk sirosis (fibrosis F4), ditunjukkan dengan AUROC 0,856 (IK 95% 0,736–0,975). Elastografi transien memiliki kemampuan diagnostik lebih baik untuk fibrosis signifikan dengan AUROC 0,761 (IK 95% 0,601–0,920) dan paling baik untuk prediksi sirosis, dengan AUROC 0,845 (IK 95% 0,722–0,968).* ***Kesimpulan:*** *ARFI merupakan prosedur evaluasi kondisi jaringan hati yang lebih praktis, dengan akurasi kemampuan diagnostik yang tidak berbeda secara signifikan dengan elastografi transien untuk menentukan derajat fibrosis hati.*

Kata kunci: *acoustic radiation force impulse (ARFI), fibrosis, elastografi transien, biopsi hepar.*

ABSTRACT

Background: *acoustic radiation force impulse (ARFI) is a new proposed noninvasive method for liver fibrosis staging. Integrated with B-mode ultrasonography, ARFI can be used to assess liver tissue condition. However its diagnostic accuracy is still being continuously evaluated. Also, there is lack of data regarding the utilization of ARFI in our population. This study aimed to evaluate the diagnostic value of ARFI as an alternative noninvasive modality for fibrosis staging in chronic hepatitis B and hepatitis C patients in our population.* ***Methods:*** *we conducted cross-sectional comparison of ARFI imaging and transient elastography on patients who underwent liver biopsy at Cipto Mangunkusumo Hospital. Fibrosis staging using METAVIR scoring system presented as*

standard reference. A total of 43 patients underwent liver biopsy was evaluated by ARFI imaging and transient elastography. Cut-off values were determined using receiver-operating characteristic (ROC). ***Results:*** *both liver stiffness determined by ARFI and transient elastography (TE) were moderately correlated with METAVIR score with value of 0.581 and 0.613, respectively (both P<0.01). Diagnostic accuracy of ARFI predicted significant fibrosis (F≥2) with area under receiver operating characteristic curve (AUROC) of 0.773 (95% CI 0.616-0.930) and even better for cirrhosis (F4 fibrosis), expressed as AUROC of 0.856 (95% CI 0.736–0.975). Transient elastography was better for significant fibrosis with AUROC of 0.761 (95% CI 0.601–0.920) and was best for prediction of cirrhosis, expressed as AUROC of 0.845 (95% CI 0.722–0.968).* ***Conclusion:*** *ARFI is provided with more convenient evaluation of liver tissue condition, and its diagnostic accuracy is not significantly different from TE for staging liver fibrosis.*

Keywords: *acoustic radiation force impulse (ARFI), fibrosis, transient elastography, liver biopsy.*

INTRODUCTION

Hepatic fibrogenesis may gradually result in cirrhosis due to the accumulation of extracellular matrix components as a response to liver injury. Thus, therapeutic decisions in chronic liver disease, regardless of the cause, should first and foremost be guided by an accurate quantification for hepatic fibrosis.[1] The examination can be done with invasive or non-invasive methods. Liver biopsy remain the gold standard in assessing the degree of liver fibrosis, which plays an important role in determining therapy for patients and monitoring the success of therapy.[2-4] However, biopsy is an invasive procedure which has weaknesses, thus non-invasive technology with excellent sensitivity and specificity was developed to assess the degree of liver fibrosis.[2] Their most important advantages are the absence of contraindications and dangerous complications for the patients, and their reproducibility.[1]

Current transient elastography (TE) enjoys great popularity. Result from previous study showed that TE had a good sensitivity and specificity, so it can be used to assess the degree of liver fibrosis, to monitor the success of therapy, and to predict mortality and severe outcome in patients with chronic liver disease.[5] Some of the non-invasive examination methods were continued to be developed, such as acoustic radiation force impulse (ARFI).[6]

Some studies comparing ARFI and TE showed various results because the baseline of the patients varied from one to another study. However, a meta-analysis of thirteen studies found that ARFI has similar accuracy as TE, but also has other advantages in other terms. ARFI is integrated into the ultrasound machine, so that the patient does not require two examinations, namely ultrasound and fibrosis measurements.[7] The failure rate as invalid measurement of ARFI has also been reported to be significantly lower than TE (0 vs 6.5%).[8,9]

However, quality criteria for ARFI to provide consistent and reproducible results is often less clear.[8] Unlike TE, the use of ultasound image to choose the positioning of region of interest in both planes will be less sensitive to the presence of ascites and to obesity. Moreover, steatosis, acute inflammation, and food intake may interfere with hepatic stiffness.[10,11] There is also no provision location and depth led to the emergence of various results on ARFI compared to TE.[6] To the best of our knowledge, there is lack of study assessing the utilization of ARFI in our population. Also, recent studies were focused on hepatitis C patients, meanwhile in practice hepatitis B patients are actually in greater proportion. Therefore, we conduct this study to gain more data in order to evaluate the diagnostic value of ARFI as an alternative noninvasive modality for fibrosis staging in chronic hepatitis B and hepatitis C patients in our population.

METHODS

This study was a diagnostic study with cross-sectional design. All subjects underwent liver biopsy, transient elastography (TE) and acoustic radiation force impulse (ARFI). This study was conducted from August 2013 to February 2014 in Cipto Mangunkusumo Hospital Jakarta. The

study population was patients aged more than 18 years old with chronic hepatitis who wanted to start treatment. Patients with non alcoholic fatty liver disease (NAFLD) or liver malignancy were excluded. Those who agreed to be a subject gave informed consent and signed it. Ethical clearance was issued by the Ethics Committee of the Faculty of Medicine, Universitas Indonesia/ Cipto Mangunkusumo Hospital, with approval number 144/H2.F1/ETIK/2014.

Liver Histology

Liver biopsy was performed under local anesthesia. Formalin was used for the specimens fixation, and then the specimens were embedded in paraffin blocks. Staining after cutting the specimens was done by the pathologist with haematoxylin and eosin. Fibrosis was assessed using masson trichrome staining, measured based on METAVIR scoring system (F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis and few septa; F3, numerous septa without cirrhosis; F4, cirrhosis). Significant fibrosis was defined as stage F2 or more.

ARFI Imaging

Acoustic radiation force impulse (ARFI) is a technology developed to measure tissue elasticity, using a shear wave velocity. ARFI can be used on a variety of tissue regions, such as the thyroid gland, mammary gland and abdominal organs such as the liver and spleen. ARFI has two methods to assess the elasticity of tissues, namely liver relative tissue stiffness and quantitative liver stiffness. Both are combined to assess tissue elasticity. ARFI is a tool that resembles the ultrasound, with probe that capable of generating vibrations. Relative liver stiffness is measured by attaching the probe to the desired region. The probe will then emit pulsations to the middle of the region with a frequency of 2.67 MHz and then the pulse wave is received back and be compared. In this examination, the stiff area is seen as a darker-colored area.

Quantitative liver stiffness was measured using a pulse emitted by a probe attached to the target region. The pulse would cause vibration 1–10 m/s at all tissue region. This vibration is called shear wave. This vibration was amplified by the coefficient that significantly higher than the longitudinal ultrasound waves. Shear wave velocity was measured by looking and analyzing the waves that cameback from various locations. Shear wave correlated with tissue elasticity, in which the faster the shear wave, the less elastic the tissue was. ARFI procedure took approximately 5 minutes for each examination.

Transient Elastography

Transient elastography (TE) is a non-invasive method to assess the degree of liver stiffness. The probe in TE works to emit amplitude vibration at medium and low frequency (50 Hz), generating an elastic shear wave that moves through the tissue under the probe. Shear wave velocity is followed and measured. The more rigid the liver tissue, the faster the shear wave will move.

Examination using TE only took a short time and could easily be tolerated by patients. The inspection carried out in the right region of the liver through the intercostal space. Patient lied in the dorsal decubitus position with the right arm to be in maximum abduction. The examination was performed 10 times, with the median value of the 10 times examination describe the elasticity of the liver.

Statistical Analysis

Data of patients who underwent liver biopsy evaluated by ARFI imaging and transient elastography were analysed. Baseline characteristics were reported descriptively, with mean and standar deviation for numeric data. Correlation between ARFI and METAVIF fibrosis stage as well as ARFI with TE were evaluated with Spearman correlation test. Cut-off values for ARFI or TE were determined using receiver-operating characteristic (ROC), respectively. Fibrosis staging using METAVIR scoring system presented as standard reference for ARFI and TE. All statistical analysis were executed with SPSS 20.0.

RESULTS

A total of 50 patients with chronic liver disease underwent liver biopsy. Among them, 5 patients were excluded due to non-hepatitis B and C etiology and 2 others due to non-representative biopsy for staging. All patients routinely attended hepatobiliary procedure room of Cipto

Mangunkusumo Hospital and were randomly selected to participate in the study. Forty-three patients underwent ARFI elastography, transient elastography, and successful liver biopsy (**Figure 1**). Characteristics of patients are shown in **Table 1**.

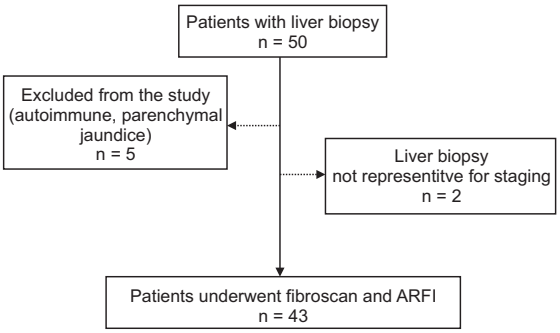

Figure 1. Diagram of chronic liver disease patients underwent liver biopsy at Cipto Mangunkusumo hospital during 12-month study period

Table 1. Patients characteristics

Characteristics	Value
Demography (n=43)	
- Male, n (%)	31 (72.1)
- Age, mean (SD), (years)	47.37 (12.67)
Laboratory data, mean (SD)	
- AST (IU/L)	71.12 (56.71)
- ALT (IU/L)	100.04 (78.12)
- Bilirubin (mg/dL)	0.83 (0.35)
- Albumin (g/dL)	4.39 (0.56)
- Platelet count (x 103/µL)	164.84 (63.23)
Chronic liver diseases, n (%)	
- Chronic hepatitis B	14 (32.6)
- Chronic hepatitis C	29 (67.4)
Fibrosis staging (METAVIR), n (%)	
- F0	0 (0)
- F1	5 (11.6)
- F2	11 (25.6)
- F3	12 (27.9)
- F4	15 (34.9)

Our study subjetcs were predominantly male with the ratio of 2,6:1 compared to female. Chronic hepatitis C was found in greater proportion (67%) than hepatitis B (33%). More than 88% patients had significant fibrosis, whereas none of our subjects was in F0 stage.

Relationship Between ARFI Liver Elasticity and METAVIR Score

Moderate correlation of increasing liver stiffness with severity of fibrosis was found. The Spearman's correlation coefficient between ARFI liver elasticity and METAVIR score was significant with value of 0.608, p<0.01 (**Figure 2**).

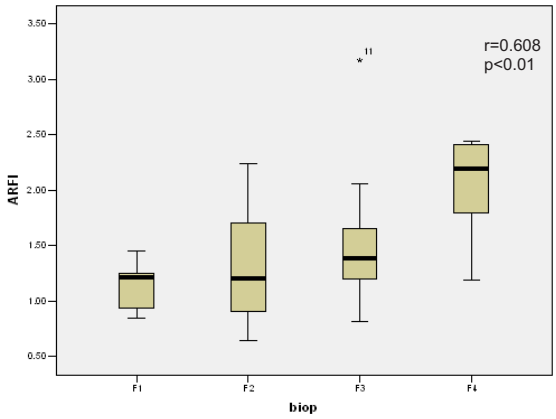

Figure 2. Correlation of ARFI and METAVIR score

We use ROC curve method to determine the cut-off for each degree of fibrosis (**Figure 3**). ARFI was able to predict significant fibrosis (F2 or more), with validity of 77.3% (95% CI AUROC = 0.616 – 0.930). The optimal median cutoff point between F1 and F2 was 1.32. At this value, ARFI elastography had a sensitivity of 68% and a specificity of 80%. ARFI showed better performance in predicting F3 or F4 fibrosis (AUROC = 78.5%, 95% CI = 0.639 – 0.932). The optimal median cut-off between F3 and F4 fibrosis was same at 1.32, with sensitivity and specificity of 82% and 73%, respectively.

ARFI predicted best for cirrhosis or non cirrhosis (F4 or <F4) (AUROC = 85.6%, 95% CI = 0.736-0.975). The optimal median cut-off was 1.71, with sensitivity and specificity of 80% and 85%, respectively. The most selective cutoff values of ARFI with corresponding sensitivity, specificity, PPV and NPV were shown in **Table 2.**

By etiology, patients with chronic hepatitis B tends to have lower cut-off values of ARFI in determining fibrosis stages compared to those

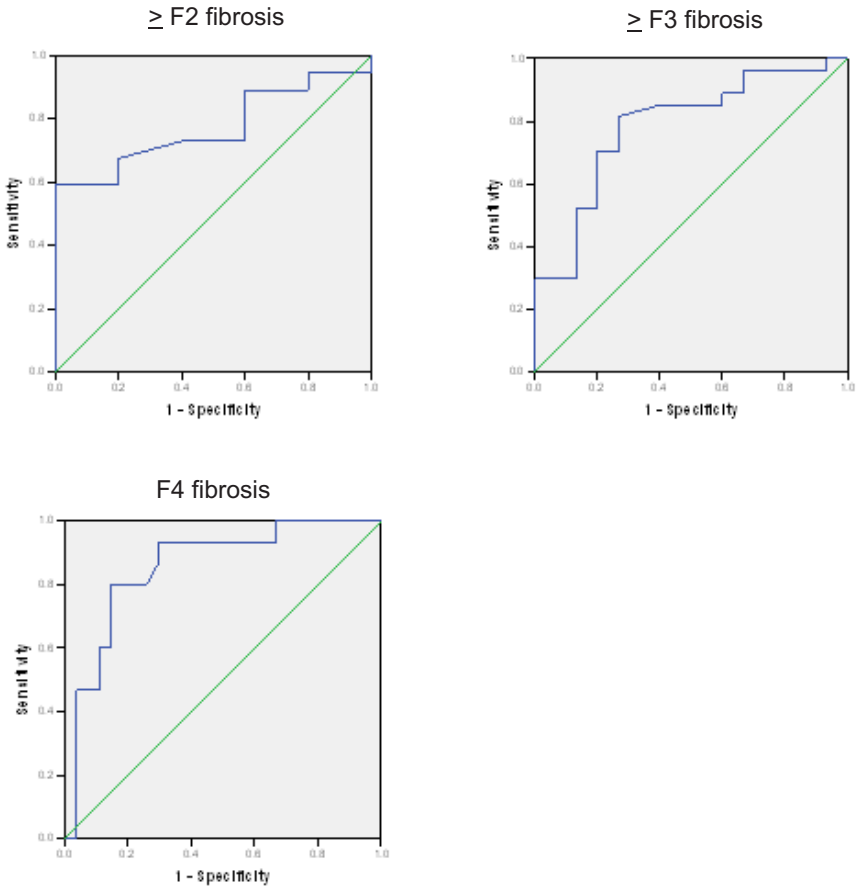

Figure 3. ROC curve for ARFI in predicting fibrosis stages

Table 2. Most selective cut-off values of ARFI and TE in determining fibrosis stages

All patients (n = 43)	Cut-off for F≥2	Se (%)	Sp (%)	PPV (%)	NPV (%)
ARFI	1.32 (m/s)	68	80	96	25
TE	8.55 (kPa)	66	80	96	24
	Cut-off for F≥3				
ARFI	1.32 (m/s)	82	73	85	67
TE	10.3 (kPa)	71	87	91	62
	Cut-off for F4				
ARFI	1.71 (m/s)	80	85	75	89
TE	12.8 (kPa)	86	82	75	92

with chronic hepatitis C. For chronic hepatitis B, the optimal median cut-off points between F1 and F2, F2 and F3, F3 and F4 were 0.97 (AUC 84.6%, 95% CI 0.650-1.042), 1.23, and 1.64 (AUC 92.5%, 95% CI 0.774-1.076), whereas in chronic hepatitis C were 1.32 (AUC 80.2%, 95% CI 0.633-0.972), 1.48, and 1.79 (AUC 80.2%, 95% CI 0.628-0.976), respectively. The most selective cut-off values of ARFI with corresponding sensitivity, specificity, PPV and NPV by etiology were shown in **Table 3**.

Relationship Between Transient Elastography and METAVIR Score

The Spearman's correlation coefficient between transient elastography liver stiffness and METAVIR score was significant with value

Table 3. Most selective cut-off values of ARFI in determining fibrosis stages by etiology

Etiology	Cut-off for F≥2	Se (%)	Sp (%)	PPV (%)	NPV (%)
Hepatitis B	0.97 (m/s)	85%	100%	100%	33%
Hepatitis C	1.32 (m/s)	79%	75%	95%	38%
	Cut-off for F≥3				
Hepatitis B	1.23 (m/s)	67%	60%	75%	50%
Hepatitis C	1.48 (m/s)	78%	80%	67%	78%
	Cut-off for F4				
Hepatitis B	1.64 (m/s)	100%	90%	80%	100%
Hepatitis C	1.79 (m/s)	72%	82%	73%	82%

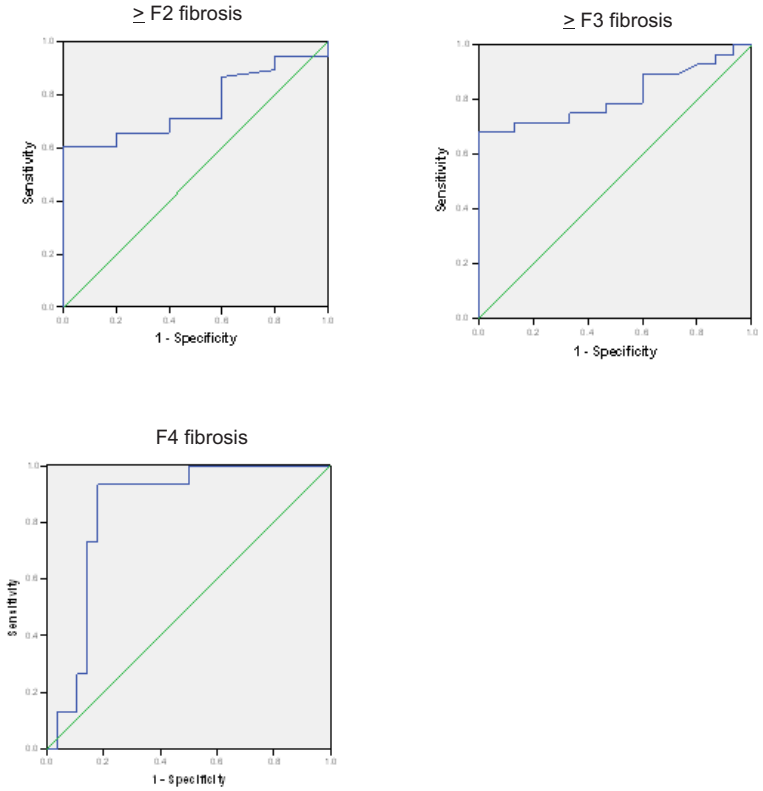

Figure 4. ROC curve for TE in predicting fibrosis stages

of 0.705 (95% CI 0.645-0.766, p<0.01).

We use ROC curve method to determine the cut-offs for each degree of fibrosis (**Figure 4**). TE predicted significant fibrosis (F2 or more), with validity of 76.1% (95% CI AUC = 0.601–0.920). The optimal cut-off point between F1 and F2 was 8.55. At this value, TE had a sensitivity of 66% and a specificity of 80%. TE showed better performance in predicting F3 or F4 fibrosis (AUC = 81.1%, 95% CI = 0.683–0.938). The optimal cut-off between F3 and F4 fibrosis was 10.3, with sensitivity and specificity of 71% and 87%, respectively. TE predicted best cirrhosis or non cirrhosis (F4 or <F4) (AUC = 84.5%, 95% CI = 0.722-0.968). The optimal cut-off was 12.8, with sensitivity and specificity of 86% and 82%, respectively. The most selective cut-off values of TE with corresponding sensitivity, specificity, PPV and NPV were shown in **Table 2**.

Applicability and Correlation of ARFI and Transient Elastography in All Patients

Both ARFI and transient elastography had been performed successfully in all patients. We

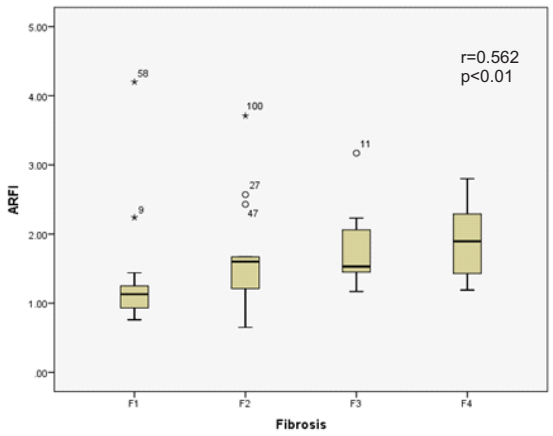

Figure 5. Correlation of ARFI and FibroScan

found significant correlation between ARFI and transient elastography, with r = 0.562, 95% CI = 0.472-0.636, p<0.01 (**Figure 5**).

DISCUSSION

Over the last 10-15 years, major efforts have been made by various groups all over the world to establish reliable and reproducible noninvasive markers of liver fibrosis to substitute liver biopsy. This study showed that the estimation of shear wave velocity using ARFI could be used as a diagnostic tool for significant fibrosis and cirrhosis, with accuracy as high as TE. We found moderate correlation between ARFI and FibroScan with r=0.562 (p <0.01), consistent with other research by Crespo et al.[12] in which ARFI correlated even stronger and more significant with FibroScan in chronic liver diseases non transplant patients with r=0.826 (p<0.001).

In regards to diagnostic accuracy of ARFI technique for each liver fibrosis, we found that ARFI elastography could predict different grades of liver fibrosis with reasonable sensitivity and specificity. The highest AUC found in later fibrosis, with 82% sensitivity and 73% specivicity for F3, and 80% and 85% for F4, respectively. Our findings agree with previous studies, a meta-analysis of thirteen studies by Bota et al.[7], which showed that ARFI was highly accurate for the diagnosis of cirrhosis compared to earlier fibrosis, with 87% sensitivity and 87% specificity, not significantly different compared to 89% and 87% for TE.

We obtained larger AUROC for patients with hepatitis B than hepatitis C, particulary in F2 (84.6% vs 80.2%) or F4 (92.5 vs 80.2%) fibrosis stage. For hepatitis C infection itself, Rizzo et al.[9] showed quite similar finding for F2 (cut-off 1.3, sensitivity 81%, specificity 70%), but larger cut-off (1.7 and 2.0), thus larger sensitivity (91% and 83%) and specificity (86% and 86%) for F3 and F4. Tai et al.[13] found that patients with hepatitis C in his study had a higher AUROC than patients with hepatitis B (0.824 versus 0.707) in predicting liver cirrhosis. Friedrich, et al.[6] also stated that liver fibrosis in hepatitis C are more homogenously distributed, compared to macronodular and episodic acute exacerbation form with more severe confluent necrosis of hepatitis B.

Elhosary, et al.[14] found that ARFI elastography was properly correlated with biochemical markers for hepatitis as it was directly correlated to AST, ALT, and INR, while it was inversely correlated to albumin, prothrombin concentration, and platelets. ARFI measurement is generally recommended after the stabilization of ALT or resolve of the inflammatory condition. Therefore, our result revealed in hepatitis B patients which was higher could be influenced by the episodic alteration of ALT and AST.[13,15]

The inclusion of ARFI in an ultrasound device could facilitate its incorporation into routine clinical practice. This ultrasound guidance is particularly helpful for ensuring that the region of interest is placed in such a way that it avoids nearby vessels and ribs, giving significant advantage. ARFI may also expand its utilization when TE is difficult to be performed, especially in patients with morbid obesity or marked ascites. Moreover, ultrasound permits the evaluation of portal diameter, splenomegaly, and liver surface, which has recently been shown to be highly accurate in the diagnosis of early cirrhosis.[12]

To the best of our knowledge, this study is the first to explore the role of ARFI as a non-invasive diagnostic technique for liver fibrosis among our population. It is important to acknowledge that the analysis was carried out in a relatively small number of patients, and it would be interesting to

see if these results also hold true in larger groups of patients. In spite of that, all enrolled patients came from all over the country, thus, we think our patient's sample represented our population well.

Our subjects had chronic liver disease either due to hepatitis B or hepatitis C virus infection. Although our findings would require further confirmation in single-etiology studies, perhaps the current study are representative of what is typically seen in routine clinical practice. However, it should be kept in mind that more heterogenous nature could be encountered in daily clinical work, especially for alcoholic, non alcoholic fatty liver disease, and autoimmune hepatitis. Thus, future studies regarding the use of ARFI evaluation per fibrosis level for those etiologies in our population will complete our current data.

CONCLUSION

In summary, we believe that there is sufficient evidence that ARFI should be taken into consideration as a non-invasive method for evaluation of liver fibrosis in patients with chronic liver disease, as ARFI is provided with more convenient evaluation of liver tissue condition and its diagnostic accuracy is similar from TE for staging liver fibrosis.

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