Comparison between Real-Time Tissue Elastography (HI-RTE) and Fibroscan in Assessment of Liver Fibrosis in Chronic HCV Patients

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Abstract

Background: Precise estimation of the degree of liver fibrosis is essential for estimating prognosis and surveillance in patients with chronic HCV. Liver fibrosis index (LFI) measured by Hitachi Real-time Elastography (HI-RTE) appeared to be effective for evaluating liver fibrosis.

Aim of Study: We aimed to evaluate the role of (HI-RTE) in staging of liver fibrosis in chronic HCV patients compared to liver stiffness measurement (LSM) by Fibroscan® and liver biopsy.

Patients and Methods: A total of 194 chronic HCV patients were recruited and subjected to baseline HCV pre-treatment assessment, including Liver function tests, complete blood picture, prothrombin time, serology for hepatitis B, HCV-RNA, and abdominal ultrasound examination. Fibroscan, HI-RTE, and finally, ultrasound guided liver biopsy, were performed for every patient.

Results: AUROCs of LSM and LFI were 0.840 and 0.721 respectively for detecting significant liver fibrosis (F 2), while in predicting advanced liver fibrosis (F 3), AUROCs were 0.904 and 0.841 respectively. Cut-off values of LFI by (HI-RTE) for predicting significant liver fibrosis (F2), advanced fibrosis (F3) and liver cirrhosis (F4), were 2.67, 2.97 and 3.35 respectively.

Conclusion: HI-RTE performs well in predicting and staging liver fibrosis in chronic HCV patients, yet, Fibroscan® remains better as a non-invasive method for assessment of liver fibrosis.

Key Words: HCV – Liver fibrosis – Fibroscan – Real time elastography.

Introduction

HEPATITIS C virus (HCV) is the cause of a significant proportion of cases of chronic liver disease, hepatocellular carcinoma (HCC), and deaths from liver disease and is the most common indication for liver transplantation (LTx) [1]. In Egypt, hepatitis C is highly endemic (up to 15% of the population) [2]. After the introduction of effective anti HCV direct-acting antiviral agents, more than 2 million patients were treated by 2018 with cure rates above 90%. However, recent screening results showed that the HCV seroprevalence among untreated persons was 4.61% [3]. Liver biopsy has traditionally been considered the gold standard for evaluating liver fibrosis in chronic hepatitis C. However, liver biopsy is an invasive procedure, and its accuracy to assess fibrosis has also been questioned concerning sampling errors and intra- and inter-observer variability that may lead to over-or understaging [4]. Also, liver biopsy does not allow dynamic evaluation of liver fibrosis over time [5]. Limitations with liver biopsy have led to the development of non-invasive methods for assessing liver fibrosis [6]. Currently, available methods rely on two different but complementary approaches [7]: A “biological” approach based on the dosage of serum biomarkers of fibrosis; and a “physical” approach based on the measurement of liver stiffness [4]. Serum biomarkers usually include routine labs combined with clinical or laboratory parameters in a specific model. Some of the most popular indices include Fib4 score, APRI score & modified APRI score [5]. Among imaging techniques, transient elastography (TE) Fibroscan® is the most widely used non-invasive method that
measures mean hepatic tissue stiffness [8]. Real-time Tissue Elastography (RTE: Hitachi Medical Co., Japan) is a relatively new method for measuring tissue elasticity. It is a simple and non-invasive method for assessing liver fibrosis, which can be performed during a routine liver ultrasound examination without the need for any additional equipment [9]. In patients with chronic hepatitis C, (HI-RTE) allows for non-invasive liver fibrosis assessment that does not vary with the sites tested or by the observer and performs better than serum fibrosis markers [10]. The performance of (RTE) appears to compare favorably with that of Fibroscan when detecting liver cirrhosis in patients with chronic liver disease [11].

Patients and Methods

Patient enrollment:

Patients were recruited from among chronic HCV patients attending to the Endemic Medicine Department and Viral Hepatitis Center, Faculty of Medicine, Cairo University, and the Hepatology clinic of the National Hepatology & Tropical Medicine Research Institute (NHTMRI) over the period from April 2014 till March 2015. These patients intended to receive antiviral treatment in the form of Pegylated Interferon/Ribavirin (PegIFN/RBV) and/or directly acting antiviral agents (DAAS). Eligible patients were 18-60 years old, seropositive for HCV-RNA, naïve to antiviral therapy with compensated hepatic synthetic functions and normal ECG and fundus examination. Key exclusion criteria were age <18, or >60 years old, seropositivity for HBsAg, associated liver pathology e.g. autoimmune hepatitis, hemochromatosis, Wilson disease or Schistosomiasis, decompensated liver disease e.g. ascites, or oesophageal varices, hepatocellular carcinoma, hematological abnormalities contraindicating liver biopsy and/or Peg-IFN/Ribavirin therapy, thyroid dysfunction, uncontrolled D.M., pregnancy or lactation, patients with organ transplants, immune mediated disease and patients receiving immunomodulatory and/or immunosuppressive drugs.

Study design and assessments:

This is a cross-sectional study conducted on 194 chronic HCV patients who intended to receive antiviral treatment in the form of Pegylated Interferon/Ribavirin (PegIFN/RBV) and/or directly acting antiviral agents (DAAS). All participants were subjected to the following:

- **Full history taking:** Including age, sex, and possible risk factors for viral acquisition.
- **Clinical examination:** Particular emphasis on manifestations suggestive of chronic liver disease and calculation of Body Mass Index (BMI) in kg/m².
- **Routine laboratory investigations:** (a) Biochemical liver profile: (Serum bilirubin, ALT, AST, alkaline phosphatase, GGT, and serum albumin). (b) Complete blood picture and PT, PC & INR. (c) Serum creatinine. (d) Viral hepatitis markers (HBsAg, quantitative HCV-RNA assay by PCR). (e) Anti-Schistosomal antibody. (f) Alpha fetoprotein (AFP).

- **Conventional ultrasound (US) examination of the liver:** Liver parenchymal echopattern is expressed as normal (homogenous), bright or coarse echopattern.
- **Imaging modalities for non-invasive assessment of liver fibrosis:**
  - **Transient Elastography (TE):** The patient is lying flat on his/her back, with the right arm tucked behind the head. The operator needs to acquire ten valid measurements, and then the Fibroscan® software calculates the median value. The success of each measurement is to be determined by the software itself [12].
  - **Real-time Tissue Elastography (HI RTE):** Patients are examined in a supine position with the right arm elevated above the head and are instructed to hold their breath. The examination is performed on the right lobe of the liver through the intercostal space. The RTE equipment displays two images simultaneously; one shows the region of interest (ROI) as a colored area, and the other indicates the conventional B-mode image. We choose an area where the tissue is free from large blood vessels and near the biopsy point. The measurement is fixed to a rectangle 30mm in length and 20mm in breadth located 510mm below the liver’s surface. The color in the ROI is graded from blue (representing hard areas) to red (representing soft areas). The scale ranged from red for components with the most significant strain (i.e., the softest components) to blue for those with no strain (i.e., the most hardened components). Green indi-
cates average strain in the ROI, and therefore intact liver tissue displayed as a diffuse homogeneous green pattern. An appearance of unevenness in the color pattern is considered to reflect a change in the liver stiffness. For quantification, all pixel data in the colored image are transferred into a histogram and binary image [13]. In this study, we used a new generation RTE technique that was developed by Hitachi Medical Systems. The technique utilizes RTE quantitative analysis software, relying on the patient’s cardiovascular pulsation to produce compression. A total of 12 quantitative parameters were calculated automatically using the updated software integrated into the HI VISION Avius ultrasound scanner [14].

Liver biopsy:

Percutaneous liver biopsies were performed under ultrasound guidance by a specialist, using 18-G disposable needles. The biopsy specimens were fixed with formalin and stained with Hematoxylin and Eosin. All of the liver biopsies were evaluated by expert pathologists, who were blinded to the patients’ clinical histories. The histologic staging of liver fibrosis was a combinatorial assessment of the amount of fibrosis and architectural disorganization using the METAVIR semiquantitative scoring system. METAVIR is demonstrating different stages of liver fibrosis as follows: F0: No fibrosis; F1: Portal fibrosis without septa; F2: portal fibrosis with rare septa; F3: Numerous septa without cirrhosis; F4: Cirrhosis, and different grades of necroinflammatory changes activity as follows: A0: No histological activity; A1: Minimal activity; A2: Moderate activity; A3: Severe activity [15].

Outcomes:

The primary outcome of the current study was to evaluate the role of Real-time Elastography (HI-RTE) in the staging of liver fibrosis in chronic HCV patients compared to Transient Elastography (Fibroscan®) and liver biopsy. Secondary outcome was to define the optimal diagnostic cut-off values for the liver fibrosis index (LFI) of Real-time Elastography for differential diagnosis of liver cirrhosis and fibrosis stage.

Statistical analysis:

Analysis of data was performed using SPSS 21 (Statistical Package for Scientific Studies) for Windows. Description of quantitative variables was in the form of mean ± Standard Deviation (SD), Median, 25th and 75th percentiles. Description of qualitative variables was in the form of numbers (No.) and percents (%). Data was explored for normality. Results indicated that data was normally distributed so parametric tests were used for comparisons. Comparison between quantitative variables was carried out by student t-test of two independent samples. Repeated measures Analysis of Variance (ANOVA) test was used instead of t-test when comparing between more than two groups of independent variables. Results were expressed in the form of p-values. Receiver Operator Characteristic (ROC) curves were constructed to assess the reliability of the noninvasive markers of liver fibrosis and to determine an appropriate score in predicting stage of liver fibrosis that gives optimal sensitivity and specificity. Area under the curve (AUC) was considered reliable if more than 65%. The significance of the results was assessed in the form of p-value that was differentiated into: Non-significant when p-value >0.05, Significant when p-value 0.05, highly significant when p value 0.01.

Results

This study was conducted on 194 chronic HCV selected patients. These patients intended to receive antiviral treatment in the form of Pegylated Interferon/Ribavirin (PegIFN/RBV) or directly acting antiviral agents (DAAS). They were selected from the Endemic Medicine Department, Faculty of Medicine, Cairo University, and Hepatology clinics of National Hepatology & Tropical Medicine Research Institute from April 2014 till March 2015 according to criteria mentioned above.

The mean age of the studied patients was 42.23 ±10.90 years and the mean BMI was 27.81±4.70. As for gender distribution of the patients, 119 (61.3%) were males and 75 (38.7%) were females.

As shown in Table (1), there was a significant statistical difference among liver fibrosis stages regarding serum albumin and platelet count where lower levels are associated with higher liver fibrosis stage (p-value 0.01). This was in contrast to serum total bilirubin, AST, ALT (p-value 0.01), and alkaline phosphatase (ALP) (p-value 0.05), where higher levels are associated with a more advanced stage of liver fibrosis. On the other hand, direct bilirubin and GGT showed no significant association with hepatic fibrosis (p-value >0.05).

As shown in Table (2) and Fig. (1), constructing the ROC curve of the used noninvasive methods in our study revealed comparable results regarding the diagnostic performance of liver stiffness measurement (LSM) by “Fibroscan®” and liver fibrosis index (LFI) by “HI-RTE” for detection of significant
liver fibrosis (F 2), with AUROCs of 0.840 and 0.721 respectively. Fibroscan® offered higher diagnostic accuracy in predicting significant liver fibrosis (F2) with significant reliability as a diagnostic tool at the cut-off value of 7.35 with a sensitivity of 80.2% and specificity of 77%. Although doing well, liver fibrosis index (LFI) by "HI-RTE" exhibited lower diagnostic performance in detecting significant fibrosis, with AUROC of 0.721. Its optimal cut-off value for predicting significant fibrosis (F2) was 2.67 with a sensitivity of 76.7% and specificity of 61%.

As shown in Table (3) and Fig. (2), analysis of the ROC curve of non-invasive methods for detection of advanced liver fibrosis (F 3) revealed comparable diagnostic performance levels for the (LSM) by Fibroscan® and LFI by (HI-RTE) with AUROCs of 0.904 and 0.734 respectively. Liver stiffness measurement (LSM) by Fibroscan® has a higher diagnostic performance level for detecting advanced liver fibrosis, with an AUROC of 0.904, with significant reliability as a diagnostic tool at the cut-off value of (8.85) with a sensitivity of 85.4% and specificity of 82.8%. Liver fibrosis index (LFI) by (HI-RTE) exhibited lower diagnostic accuracy than Fibroscan® in detecting advanced fibrosis (F3) with AUROC of 0.734 with its best cutoff value at (2.97) with a sensitivity of 63.4% and specificity of 71 %.

As shown in Table (4) and Fig. (3), on constructing ROC curve of non-invasive methods for detection of liver cirrhosis (F4), it revealed comparable diagnostic performance levels for (LSM)
by Fibroscan® and LFI by (HIRTE) with AUROCs of 0.975 & 0.841 respectively. LSM by Fibroscan® exhibited the a better diagnostic performance level for cirrhosis detection, with an AUROC of 0.975. Therefore, (LSM) by Fibroscan® was the optimal predictive method for detecting HCV-related cirrhosis with significant reliability as a diagnostic tool at the cut-off value of (12.75) with a sensitivity of 100% and specificity of 91%. Liver fibrosis index (LFI) by (HI-RTE) showed a lower diagnostic performance level with AUROC of 0.841. The optimal cut-off value of LFI for detection of liver cirrhosis (F4) was (3.35) with a sensitivity of 88.9% and specificity of 76.8%.

Table (3): Indices of non-invasive methods for detection of advanced liver fibrosis (F 3).

<table>
<thead>
<tr>
<th>Test Result Variable(s)</th>
<th>AUC</th>
<th>Std. Error</th>
<th>Asymptotic 95% Confidence Interval</th>
<th>Best Cut-off</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Fibroscan” Stiffness (kPa)</td>
<td>0.904</td>
<td>0.024</td>
<td>0.858 0.950</td>
<td>8.85</td>
<td>85.4%</td>
<td>82.8%</td>
<td>&lt;0.001 **</td>
</tr>
<tr>
<td>&quot;RTE” Liver fibrosis index (LFI)</td>
<td>0.734</td>
<td>0.046</td>
<td>0.644 0.825</td>
<td>2.97</td>
<td>63.4%</td>
<td>71%</td>
<td>&lt;0.001 **</td>
</tr>
</tbody>
</table>

*p<0.05 (significant).  *p<0.01 (Highly significant).  
AUC: Area under the curve.  Std error: Standard error.  kPa: Kilopascal. RTE: Real time elastography. LFI: Liver fibrosis index.

Table (4): Indices of non-invasive methods for detection of liver cirrhosis (F4).

<table>
<thead>
<tr>
<th>Test Result Variable(s)</th>
<th>AUC</th>
<th>Std. Error</th>
<th>Asymptotic 95% Confidence Interval</th>
<th>Best Cut-off</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Fibroscan” Stiffness (kPa)</td>
<td>0.975</td>
<td>0.012</td>
<td>0.952 0.998</td>
<td>12.75</td>
<td>100%</td>
<td>91%</td>
<td>&lt;0.001 **</td>
</tr>
<tr>
<td>&quot;RTE” Liver fibrosis index (LFI)</td>
<td>0.841</td>
<td>0.054</td>
<td>0.734 0.947</td>
<td>3.35</td>
<td>88.9%</td>
<td>76.8%</td>
<td>&lt;0.001 **</td>
</tr>
</tbody>
</table>

*p<0.05 (significant).  *p<0.01 (Highly significant).  
AUC: Area under the curve.  Std error: Standard error.  kPa: Kilopascal. RTE: Real time elastography. LFI: Liver fibrosis index.
Discussion

Routinely used laboratory parameters as markers of liver fibrosis:

This study shows significant relation between liver fibrosis and several routinely used laboratory parameters, especially serum AST, bilirubin, albumin level, and platelet count.

There was a significant relation between platelet count and severity of liver fibrosis, where lower platelet count is with higher grades of liver fibrosis. Platelet count decreased with significant liver fibrosis (F2), advanced fibrosis (F3), and liver cirrhosis (F4). This is consistent with Kandemir et al., [16] and Hung-Wei et al., [17].

Our results support the role of serum AST level as a good predictive variable for detection of liver fibrosis, where higher levels are associated with more advanced stages of liver fibrosis in CHC patients, which is in concordance with Drees et al., [18]. Previous studies also show that low AST values significantly correlate with less severe histological parameters and extent of liver fibrosis, especially when combined with platelet count [19], age, total cholesterol level, insulin resistance, and past alcohol intake [20].

Detection of significant liver fibrosis:

Liver fibrosis index (LFI) by (HI-RTE) showed significantly high diagnostic accuracy for differentiating significant fibrosis (F2-F4 versus F0-F1) with the area under the receiver operating characteristic (AUROC) curve of (0.721) with sensitivity 76.7% and specificity 61% at the cut-off value 2.67. This agrees with results obtained by Ge et al., [21].

This study demonstrated comparable performance levels among the used methods in detecting significant fibrosis (F2). Liver stiffness measurement (LSM) by Fibroscan® exhibited a higher diagnostic performance level with (AUROC) 0.840 versus 0.721 for LFI by (RTE) with significant reliability as a diagnostic tool for prediction of significant liver fibrosis at the cut-off value 7.35 with a sensitivity of 80.2% and specificity of 77%. This is correspondent with the study of Ferraioli et al., [22], which revealed that, on distinguishing severe fibrosis (F3) than LFI by (RTE) and APRI with (AUROC) 0.95 for (LSM) by Fibroscan® versus 0.80 and 0.89 for LFI by (RTE) and APRI respectively.

These results mean that LFI by (RTE) in our study appears to be inferior to (LSM) by Fibroscan® which is contradictory with Meng et al., [23], who reported that Real-time elastography (LFI) is an effective method for assessing liver fibrosis, with diagnostic performance similar to that of transient elastography by Fibroscan®.

Detecting liver cirrhosis:

This study revealed that LFI by (HI-RTE) has significant high diagnostic accuracy in differentiating liver cirrhosis (F4 versus F0-F3) at the cut-off value of 3.35 with 88.9% sensitivity and 76.8% specificity. This agrees with Ge et al., [14], who reported that (LFI) at a cut-off value of 3.25 for diagnosing cirrhosis stage resulted in a sensitivity of 100%, and specificity of 88.9%, and an accuracy value of 90.8%.

By comparing LFI by (RTE) to (LSM) by Fibroscan® as non-invasive methods for detecting liver cirrhosis (F4), we found that both methods exhibited comparable diagnostic performance levels. (LSM) by Fibroscan® has higher diagnostic performance with (AUROC) 0.975 versus 0.841 for (LFI) by (RTE) with significant reliability of Fibroscan® as a diagnostic tool for prediction of liver cirrhosis (F4) at the cutoff value 12.75 kPa with a sensitivity of 100% and specificity of 91% which is consistent with Elsharkawy et al., [26], that validated the cut-off value of 12.2kPa by Fibroscan® for detection of liver cirrhosis in genotype 4 CHC patients. This is also in agreement (LFI) calculated by RTE showed a very good diagnostic performance to predict advanced fibrosis (F3-F4 versus F0-F2) in CHC patients at a cut-off value of 2.38 with remarkable sensitivity and NPV.

Similarly, our results showed that (LFI) exhibited a high diagnostic performance level for predicting advanced fibrosis at a cut-off value of 2.97 with a sensitivity of 63.4% and specificity of 71%.

By comparing LFI by (RTE) to (LSM) by Fibroscan® as non-invasive methods for diagnosing advanced fibrosis (F3) in studied patients revealed that both of them showed comparable diagnostic performance levels. Liver stiffness measurement (LSM) by Fibroscan® was superior to LFI by (RTE) with (AUROC) 0.904 versus 0.734 for LFI by (RTE). This is consistent with Ferraioli et al., [22], who concluded that TE by (Fibroscan®) offered higher diagnostic performance in assessing severe fibrosis (F3) than LFI by (RTE) and APRI with (AUROC) 0.95 for (LSM) by Fibroscan® versus 0.80 and 0.89 for LFI by (RTE) and APRI respectively.
with the study of Ferraioli et al., [22], which stated that (LSM) by Fibroscan® exhibited a higher diagnostic performance level in predicting liver cirrhosis than that of LFI by (RTE) and APRI with (AUROC) 0.97 for (LSM) by Fibroscan® versus 0.80 and 0.84 for LFI by (RTE) and APRI respectively, which also, means that LFI by (RTE) was inferior to Fibroscan® and APRI in predicting liver cirrhosis and this is matching with our study results.

Conclusion:
Liver fibrosis index (LFI) measured by real-time elastography (HI-RTE) appears to correlate well with the histological grade and is clinically applicable for detecting liver fibrosis. LFI by HI-RTE is nearly as effective as liver stiffness measurement (LSM) by Fibroscan®. Both of them showed high reliability as noninvasive methods in predicting and staging liver fibrosis in CHC patients with comparable diagnostic performance levels. Nevertheless, LSM by Fibroscan® offered higher diagnostic performance in assessing liver fibrosis. However, we believe that further studies may increase the predictive value of real-time elastography in assessing liver fibrosis.

References


