Diagnostic Performance of Acoustic Radiation Force Impulse Imaging in Evaluating Liver Fibrosis in Patients with Chronic Hepatitis B Infection: A Cross-Sectional Study

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Abstract

Background Acoustic radiation force impulse point shear wave elastography (ARFI-pSWE), measuring shear-wave velocity (SWV), has been utilized to examine the liver stiffness caused by different etiologies. However, information on its reliability in staging liver fibrosis in chronic hepatitis B (CHB) patients is scarce.

Purpose The aim of the study is to examine the diagnostic performance of ARFI-pSWE and determine the optimal SWV cut-off values to predict significant fibrosis (F ≥ 2) and cirrhosis (F4) in CHB patients.

Material and Methods All 114 adult CHB patients visiting the University Medical Center, Ho Chi Minh City, Vietnam between February 2019 and March 2021 underwent liver stiffness measurement using ARFI-pSWE and FibroScan. SWV results were tested against FibroScan for sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). The area under the receiver operating characteristic (AUROC) curve was used to identify the optimal SWV cut-off values.

Results There was a strong agreement between ARFI-pSWE and FibroScan ($r = 0.92$, $p < 0.001$). The optimal SWV cut-off value for detecting significant fibrosis was 1.37 m/s with an AUROC of 0.975, sensitivity of 83.3%, specificity of 100%, PPV of 100%, and NPV of 81%. The optimal cut-off value for predicting cirrhosis was 1.70 m/s with an AUROC of 0.986, sensitivity of 97%, specificity of 93%, PPV of 95%, and NPV of 96%.

Conclusion ARFI-pSWE could be an effective technique for evaluating liver fibrosis in CHB patients. SWV cut-off values of 1.37 and 1.70 m/s could be used to diagnose significant fibrosis and cirrhosis, respectively.
Introduction

Chronic hepatitis B (CHB) infection affects approximately 240 million people worldwide. Human immune response to the virus may result in liver fibrosis and cirrhosis. Hence, it has been suggested that liver fibrosis assessment should be performed routinely in patients with CHB infection. Several invasive and non-invasive assessment methods have been used to detect liver fibrosis. Liver biopsy, which is an invasive technique, is considered the gold standard to evaluate liver fibrosis and cirrhosis. However, repeated biopsies, which are required for monitoring the disease course, are impractical because of their invasiveness and potential complications. Therefore, non-invasive assessment methods, such as imaging techniques, have been extensively utilized in chronic viral hepatitis infection. Of these imaging techniques, transient elastography (FibroScan; Echosens, France), which is a rapid and reproducible ultrasound-based technique, has been approved by the United States Food and Drug Administration as a reference method for liver stiffness assessment in chronic liver diseases. In the updated guidelines of the European Association for the Study of Liver in 2021, FibroScan (FS) remains the most validated non-invasive method in evaluating liver fibrosis.

It is noted that FS is not the only ultrasound-based technique used for liver stiffness measurement but also has several disadvantages. First, it needs specific equipment that performs only elastography without visually determining the site of measurement. Second, the right lobe is the only part of the liver that could be measured. Finally, obesity and ascites could be factors affecting the result of the examination. Meanwhile, point shear wave elastography (pSWE) using acoustic radiation force impulse (ARFI) could overcome the above disadvantages of TE. It is another effective, non-invasive method that measures the velocity of the shear-wave propagation in liver tissue to detect liver fibrosis. ARFI technique has been integrated into a conventional ultrasound that allows assessing liver morphology at the same time. In addition, ARFI allows the examiner to choose and adjust the depth of the region of interest, and the examination could also be performed in patients with obesity or ascites. Several studies conducted on mixed populations with different viral hepatitis, in which individuals with chronic hepatitis C (CHC) infection were predominant, have demonstrated a strong agreement between ARFI-pSWE and liver biopsy in liver fibrosis evaluation. In our country, studies evaluating the role of ARFI-pSWE in detecting liver fibrosis and cirrhosis in patients with CHB infection are scarce. The presenting study aimed to examine the agreement between ARFI-pSWE and FS and establish the optimal cut-off values of shear-wave velocity (SWV) in predicting significant fibrosis (F ≥2) and cirrhosis (F4) in CHB patients.

Materials and Methods

Study Design

A cross-sectional study was conducted between February 2019 and March 2021 at the Liver Clinic, University Medical Center, Ho Chi Minh City, Vietnam. All patients with CHB infection who visited the Liver Clinic during this period were invited to participate in the study. Written informed consent was obtained from all study participants. The study was approved by the Ethics Committee of the University of Medicine and Pharmacy at Ho Chi Minh City, Vietnam (Reference No. 71/2019/HĐ-DHYD) and was performed in accordance with the ethical principles of the Declaration of Helsinki. The inclusion criteria included patients aged 18 years or older, diagnosed with CHB infection (hepatitis B surface antigen is positive for >6 months), disregarding undergoing antiviral therapy. The exclusion criteria included patients with ascites, hepatocellular carcinoma, pregnancy, hepatitis B infection, heavy alcohol use (consumption of >3 drinks/d for men and >2 drinks/d for women for >5 years), moderate to severe steatohepatitis (Controlled Attenuation Parameter measured by FibroScan S≥52), or refusal to participate in the study.

Sample Size

According to the study of Kircheis et al., Pse (sensitivity of ARFI in detecting $F \geq 2$) and Psp (specificity of ARFI in diagnosing $F = 4$) were 0.91 and 0.97, respectively. Based on the result of Göbel et al., $P_{dis.F \geq 2}$ (the percentage of $F \geq 2$ in CHB patients) and $P_{dis.F4}$ (the rate of $F4$ in CHB patients) were 36 and 18%, respectively. Sample size was calculated using these results of previous workers. Thus, for a two-tailed test, 95% CI and an error of 5%, sample size calculated for 91% sensitivity and 36% prevalence of $F \geq 2$ was 88 subjects and for 97% specificity and 18% prevalence of F4 was 14 subjects. We studied 123 subjects.

Laboratory and Imaging Tests

Participants were asked to undertake blood tests and elastography measurements on the day they agreed to participate in the study. Blood tests included complete blood count, serum creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transpeptidase (GGT). Liver fibrosis assessment involved the use of FS and ARFI-pSWE performed by two qualified physicians. Each designated physician utilized one of the two techniques and was unaware of the remaining physician’s examination results. The FS and ARFI protocols were in line with the guidelines of the World Federation for Ultrasound in Medicine and Biology.

FibroScan

FS was performed using FibroScan Compact 530 (Echosens, Paris, France) with the M-probe (standard probe—transducer frequency 3.5 MHz). An FS session was regarded as successful and liver stiffness measurements were considered reliable when the obtained shots satisfied the following criteria: (1) at least 10 shots obtained in the FS session were valid; (2) the ratio of the number of valid shots to the total number of shots obtained in the session was greater than 60%; and (3) the interquartile range divided by the median FS value was less than 30%. For each session, the median value of the valid
measurements was used as the representative FS result for categorizing liver fibrosis stages and determining the agreement between ARFI-pSWE and FS. Fibrosis stages were categorized based on the METAVIR classification. The FS cut-off values used to categorize fibrosis stages included <7 kPa (F0–1, no-mild liver fibrosis), 7 to <9.5 kPa (F2, moderate liver fibrosis), 9.5 to <11 kPa (F3, severe liver fibrosis), >11 kPa (F4, liver cirrhosis). Based on FS measurements, patients were classified into three groups including group 1 (patients with F0 or F1), group 2 (patients with F2 or F3), and group 3 (patients with F4).

Acoustic Radiation Force Impulse
ARFI imaging was performed using ACUSON Juniper Ultrasound System (Siemens Medical Solutions, Erlangen, Germany) with the Virtual Touch Tissue Quantification mode and an abdominal curved transducer. A measurement depth of 2 cm below the liver capsule was standardized for measuring SWV. For each ARFI session, measurement values obtained from each patient were regarded as reliable when there were at least 10 valid measurements and the ratio of the interquartile range value to the median (IQR/M) < 30%. The median value of the valid measurements was considered the representative SWV result that was used to identify the agreement between ARFI-pSWE and FS.

Statistical Analysis
Data were analyzed using R software (version 3.5.2). Continuous variables were expressed as mean ± standard deviation, and categorical variables were represented as absolute count and proportion. For examining the association between SWV values and liver fibrosis stages, one-way ANOVA and post-hoc analysis, using the Tukey method were used to determine whether there were significant differences regarding the SWV mean values between three fibrosis stage groups. Assessing the agreement between FS and ARFI-pSWE in diagnosing liver fibrosis was based on inter-rater reliability (Pearson’s correlation coefficient and Kappa value). Evaluating the diagnostic performance of ARFI-pSWE and identifying the SWV cut-off values for predicting significant fibrosis (F ≥ 2) and cirrhosis (F4) were relied on generating the receiver operating characteristic (ROC) curves as well as calculating the area under the ROC (AUROC), sensitivity (Sens), specificity (Spec), positive predictive value (PPV), and negative predictive value (NPV). The optimal cut-off values were computed using the method that maximized the sum of sensitivity and specificity. The significance level was set at p ≤ 0.05.

Results
A total of 123 participants were enrolled in this study, among whom nine patients were excluded due to failure to meet the inclusion criteria (Fig. 1). Hence, 114 participants with a mean age of 52 ± 10 years were included in the analysis (Table 1). Among these 114 patients, 69 (61%) were males, 97 (85%) received antiviral therapy, 17 (15%) were treatment-naive CHB individuals, 28 (25%) tested positive for hepatitis B e antigen (HBeAg), and 44 (39%) had a platelet count lower than 150.0 × 10^9/L. The mean AST, ALT, and GGT values were 35.7 ± 13.1 U/L, 29.7 ± 14.5 U/L, and 43.3 ± 38.6 U/L, respectively. The mean platelet count was 169.3 ± 68.0 (×10^9/L).

Association between SWV Measurements and Fibrosis Stages
The proportion of patients in fibrosis stage group 1 was 37% (42/114), and those of patients in groups 2 and 3 were 36%...
Table 2 Distributions of mean shear-wave velocity (SWV) values by liver fibrosis stages

<table>
<thead>
<tr>
<th>Fibrosis stages</th>
<th>Group 1 (F0 + F1) (n = 42)</th>
<th>Group 2 (F2 + F3) (n = 41)</th>
<th>Group 3 (F4) (n = 31)</th>
<th>p-Valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWV mean ± SD (m/s)</td>
<td>1.22 ± 0.17</td>
<td>1.54 ± 0.13</td>
<td>2.30 ± 0.56</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

aOne-way ANOVA.

Fig. 2 Distributions of shear-wave velocity (SWV) values by liver fibrosis stages.

Fig. 3 Correlation between shear-wave velocity (SWV) values and FibroScan values (r = 0.92, 95% CI: 0.88–0.94, p < 0.001).

Table 3 Post-hoc analysis of the mean shear-wave velocity (SWV) values of different fibrosis stages

<table>
<thead>
<tr>
<th>Between groups</th>
<th>Mean difference</th>
<th>95% CI</th>
<th>p-Valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 2 to Group 1</td>
<td>0.32</td>
<td>0.16–0.49</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Group 3 to Group 1</td>
<td>1.08</td>
<td>0.91–1.26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Group 3 to Group 2</td>
<td>0.76</td>
<td>0.58–0.94</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

aTukey post-hoc analysis.

Discussion

In our study, significant fibrosis was grouped into group 2 that was comprised of F2 and F3, and group 3 that was comprised of F4, because moderate fibrosis and cirrhosis have been considered as the two most important landmarks in managing CHB patients.24,25 The percentage of patients with $F \geq 2$ in our study was 63%, higher than the rates of significant fibrosis reported in three large systematic review and meta-analysis studies ranging from 49.4 to 61.1%.26–28 Unlike our study, these reviews included studies conducted on heterogeneous groups of CHB patients in different continents, including Asia, Europe, America, and Africa.26–28 The dissimilarities in the demographic characteristics of study cohorts may result in the differences in the proportion of
patients with significant fibrosis between our study and the three reviews.

Regarding the association between SWV results and fibrosis stages, we found that the mean SWV values increased significantly in response to the increase in the severity of liver fibrosis. Among the three liver fibrosis groups, patients without or with mild fibrosis had the lowest mean SWV value (1.22 ± 0.17 m/s). The highest mean value was 2.30 ± 0.56 m/s and was observed in cirrhosis patients. The association between SWV values and liver fibrosis stages has been reported in several studies, even though they examined liver fibrosis caused by etiologies rather than CHB.\(^7\,11\,16\,29\)

Our study also revealed that SWV values strongly agreed with FS measurements (\(r = 0.92\)). Despite exclusively focusing on CHB patients, our finding is consistent with studies that enrolled patients with chronic liver disease caused by different etiologies.\(^13\,16\) The agreement between ARFI-pSWE and FS from our study indicates that ARFI-pSWE may be an alternative to FS in evaluating liver fibrosis in CHB patients.

The optimal SWV cut-off value for predicting significant fibrosis (\(F \geq 2\)) in our study (1.37 m/s) is higher than those reported by Kircheis et al (1.29 m/s) and Friedrich-Rust (1.39 m/s).\(^16\,30\) Meanwhile, our optimal SWV cut-off value for detecting cirrhosis (1.70 m/s) is higher than that reported by Kircheis et al (1.6 m/s) but smaller than the cut-off recommended by Ye et al (1.88 m/s) (\(\rightarrow\) Table 5).\(^16\,31\) The exclusive inclusion of CHB patients in our study might make our cut-off values inconsistent with those reported by studies that included patients with chronic liver disease caused by different etiologies.\(^32\) Indeed, it has been documented that, in the same fibrosis stage, CHB patients had a mean SWV value significantly lower than that of CHC patients.\(^32\) Besides, the dissimilarity in SWV cut-off values may be attributable to the references in the reference methods used to distinguish liver fibrosis stages. Our study used FibroScan, while Friedrich-Rust et al utilized liver biopsy to diagnose liver fibrosis and Ye et al relied on a combination of upper endoscopy and liver biopsy to diagnose cirrhosis.\(^30\,31\) Despite the inconsistency in the cut-off values, our finding of the high accuracy of ARFI-pSWE in evaluating liver fibrosis is in accordance with other studies.\(^3\,13\,16\) Our Kappa values of 0.863 for diagnosing significant fibrosis and 0.849 for detecting cirrhosis confirmed a high degree of agreement between ARFI-pSWE and FS. The high diagnostic accuracy of ARFI-pSWE indicates that this technique may be a reliable and effective diagnostic method that could be used as a substitute for FS to differentiate liver fibrosis stages.

Our study has some limitations. Since our study only included CHB patients, the study findings may not be generalizable to patients with chronic liver diseases caused by other etiologies. Hence, future research is needed to replicate this study in populations with chronic liver diseases caused by other etiologies. Nevertheless, it has been documented that there are differences in SWV values between CHB patients and CHC patients that have the same fibrosis stage.\(^32\) Due to excluding patients with CHC infection, the association

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study population</th>
<th>Standard of liver fibrosis assessment</th>
<th>(F \geq 2)</th>
<th>F4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liem et al (2012)</td>
<td>CHB, CHC patients, healthy controls</td>
<td>FibroScan</td>
<td>Cut-off: 1.25 m/s</td>
<td>Sens: 83.7% Spec: 87.3%</td>
</tr>
<tr>
<td>Kircheis et al (2012)</td>
<td>Chronic hepatitis patients, healthy controls</td>
<td>FibroScan</td>
<td>Cut-off: 1.29 m/s</td>
<td>Sens: 91.4% Spec: 92.6%</td>
</tr>
<tr>
<td>Ye et al (2012)</td>
<td>CHB patients</td>
<td>Liver biopsy</td>
<td>Cut-off: 1.88 m/s</td>
<td>Sens: 95.7% Spec: 91.8%</td>
</tr>
<tr>
<td>Friedrich-Rust et al (2013)</td>
<td>Chronic hepatitis patients</td>
<td>Liver biopsy</td>
<td>Cut-off: 1.39 m/s</td>
<td>Sens: 50% Spec: 90%</td>
</tr>
</tbody>
</table>

Table 4 Performance of shear-wave velocity (SWV) quantification in evaluating significant fibrosis and cirrhosis tested against FibroScan

<table>
<thead>
<tr>
<th></th>
<th>Area under the receiver operating characteristics (AUROC)</th>
<th>Cut-off value (m/s)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive predictive value (%)</th>
<th>Negative predictive value (%)</th>
<th>Kappa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Significant fibrosis ((F \geq 2))</td>
<td>0.975</td>
<td>1.37</td>
<td>83.3</td>
<td>100</td>
<td>81</td>
<td>0.863</td>
<td></td>
</tr>
<tr>
<td>Cirrhosis (F4)</td>
<td>0.986</td>
<td>1.70</td>
<td>97</td>
<td>93</td>
<td>95</td>
<td>96</td>
<td>0.849</td>
</tr>
</tbody>
</table>
between SWV values and fibrosis stages demonstrated in our study is reliable and specific to CHB. In addition, since most of our participants (85%) received antiviral treatment, our findings also shed light on the use of ARFI-pSWE in evaluating fibrosis stages in CHB patients receiving antiviral therapies.

In conclusion, ARFI-pSWE strongly agreed with FibroScan in detecting liver fibrosis in CHB patients. ARFI-pSWE can be a reliable alternative to assess liver fibrosis in CHB patients, regardless of whether patients have received antiviral treatment. The SWV cut-off values of 1.37 and 1.70 m/s are suggested to diagnose significant fibrosis and liver cirrhosis, respectively. Future studies are needed to evaluate the role of ARFI-pSWE in monitoring fibrosis improvement in response to antiviral treatment among patients with CHB.

Authors’ Contributions
The trial was designed by H.H.B., together with V.H.V., S.T. P., P.T.Q, B.D.N. collected the data. C.D.N. analyzed the data. H.H.B., V.H.V., and C.D.N. wrote the manuscript. H.H.B., C. D.N., S.T.P., P.T.Q., and B.D.N. revised the manuscript. All authors approved the final version of the manuscript.

Presentation at a Meeting
This study was presented as an e-poster in Singapore Hepatology Conference 2021, October 11 to 15th.

Research Ethics and Patient Consent
Written informed consent was obtained from all study participants. The study was approved by the Ethics Committee of the University of Medicine and Pharmacy at Ho Chi Minh City, Vietnam (Reference No. 71/2019/H-DHYD) and was performed in accordance with the ethical principles of the Declaration of Helsinki.

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Conflict of Interest
None declared.

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