Diagnosis of liver fibrosis in patients with hepatitis B–related liver disease using ultrasound with wave-number domain attenuation coefficient

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ABSTRACT

Background/Aims: The importance of identifying the stage of liver fibrosis has motivated the development of non-invasive methods. This study aimed to evaluate the applicability of ultrasound analysis involving the wave-number domain attenuation coefficient (W-Ac) in the non-invasive quantitative differentiation of liver fibrosis.

Materials and Methods: This was a prospective study of inpatients with hepatitis B–related liver disease treated between October 2016 and January 2018. In ultrasound, the echo from the near-field liver tissue was selected as the reference signal. The W-Ac of liver tissues was based on the fast Fourier transform of the acquired post-beamforming radio frequency signals. These values were compared with fibrosis from biopsy METAVIR score results. A receiver operating characteristic (ROC) curve tested the W-Ac method.

Results: A total of 46 patients were enrolled, including 27 males and 19 females. Fibrosis was stage F0 in 12 patients, F1 in 13 patients, F2 in 10 patients, F3 in 7 patients, and F4 in 4 patients. W-Ac increased with the progression of liver fibrosis up to stage F3. There were differences between F0 and F4 stages ($p<0.001$) and between any 2 stages of fibrosis ($p<0.05$), except for stages F3 and F4. There was a significant correlation between W-Ac and METAVIR score ($r=0.795$, $p<0.001$). W-Ac differed between non-fibrosis (F0) and fibrosis (F1–F4) groups ($p<0.001$) and in the normal (F0), early fibrosis (F1–2), and late fibrosis groups (F3–4) ($p<0.001$). ROC area under the curve was 0.890, and at a cut-off of 0.12153, sensitivity was 0.706 and specificity was 0.830.

Conclusions: W-Ac allowed assessment of liver fibrosis in clinical practice.

Keywords: Liver cirrhosis, ultrasonography, Fourier analysis, disease progression, diagnosis

INTRODUCTION

Liver fibrosis is a common consequence of chronic liver disease, caused by the increased deposition of fibrotic tissues within the liver. Cirrhosis, as the final stage of liver fibrosis, may cause various complications in patients, including portal hypertension, ascites and variceal bleeding, and ultimately organ failure and even death. However, early liver fibrosis, if treated properly, may regress or even recover completely (1-5). Therefore, it is important to distinguish different stages of liver fibrosis and provide clinicians with a range of effective medications.

Although liver biopsy remains the gold standard for exploring the stage of liver fibrosis, its application is limited because of its invasive nature; side effects, such as bleeding; and other limitations, such as inapplicability for repeated assessments. Accordingly, development of non-invasive assessment methods for liver fibrosis, such as serological examination (6–9) and imaging (10–15), have been promoted. Currently, elastography techniques, including transient elastography (16–18), acoustic radiation force impulse imaging (19,20), and shear wave elastography (21,22), are the most widely used imaging techniques for non-invasive assessment of liver fibrosis. Nevertheless, different factors influence the accuracy and applicability of these techniques, including obesity, ascites, hepatic inflammation, congestion, and the operator's experience (23). Therefore, the effectiveness of these non-invasive methods still needs to be validated.

Alternative approaches to the analysis of ultrasound imaging of fibrosis may provide more effective non-invasive fibrosis staging. Pathological changes affect the propagation of ultrasonic waves, which can be quantified by measuring the speed of sound, attenuation coefficient (Ac), backscatter coefficient, and other parameters. In this regard, Meziri et al (24). conducted several studies to determine the potential of these parameters in discriminating between different stages of liver fibrosis in vitro (25–27). Their studies showed that changes in acoustic parame-

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ters may present a more objective assessment of tissue attenuation composition, which is related to the stage of liver fibrosis in vitro. However, those in vitro studies were on isolated liver specimens and were not performed in a similar manner to clinical ultrasound. Generally, considering the extremely complex structure of tissues in the human body, there are differences between in vivo and in vitro experiments. Therefore, it is essential to study the applicability of Ac in determining the stage of liver fibrosis in vivo.

The aim of this study was to investigate the clinical application of Ac in ultrasound staging of liver fibrosis. We hypothesized that using the wave-number domain Ac (W-Ac) method to process the post-beamforming data of ultrasound can determine the effect of the liver parenchyma on the attenuation of ultrasound signals and eliminate the effect of tissues outside the liver. Therefore, we acquired the post-beamformed radio frequency (PRF) data from clinical sonographs, and individual differences and anisotropy of tissues were investigated.

MATERIALS AND METHODS

Study Design and Patients

This was a prospective study of inpatients with hepatitis B virus (HBV)-related liver disease that underwent B-mode ultrasound examination with collection of post-beamforming data and liver biopsy to determine follow-up treatment between October 2016 and January 2018 at The First Affiliated Hospital of Anhui Medical University. Patients were excluded according to the following criteria: 1) patients whose PRF data analysis failed or biopsy specimens did not meet the quality requirements of pathological diagnosis and 2) body mass index.

This study was approved by the Institutional Ethics Committee of our hospital. After the study design was explained, the patients completed the written informed consent before the study.

W-Ac method

All ultrasound examinations were performed using VINNO 70 diasonograph (Vinno, Jiangsu, China) with an X4-12L linear array probe (central frequency, 10 MHz), which can export raw post-beamforming data. A high-frequency linear array probe was used for high resolving power.

Both ultrasound examination and post-beamforming data collection were conducted by an expert operator 1 hour before liver biopsy. All participants fasted for more than 6 hours, and data collection was performed in the supine position. The scanning depth was maintained at 6 cm with a single focal point at 3 cm. The post-beamforming data from the right lobe were collected from the right intercostal region while trying to avoid vessels and bile ducts.

To determine the effect of the liver parenchyma on the attenuation of ultrasound signals and eliminate the effect of tissues outside the liver, we used the W-Ac method to process the post-beamforming data, in which the liver parenchyma in the nearer field and in the deeper field were selected as the reference region and the region of interest (ROI), respectively. W-Ac was determined when the ultrasound signal traveled through the liver tissue within a certain distance. Then the relationships between W-Ac and histological score (METAVIR score) (28) of liver fibrosis were analyzed. The reference region was selected under the liver capsule (Figure 1) with a 100-line scan width. The ROI was selected at a depth of 1 to 2 cm below the reference region (Figure 1), with the same width as the reference region. W-Ac was calculated after Fourier transforming the post-beamforming signals.

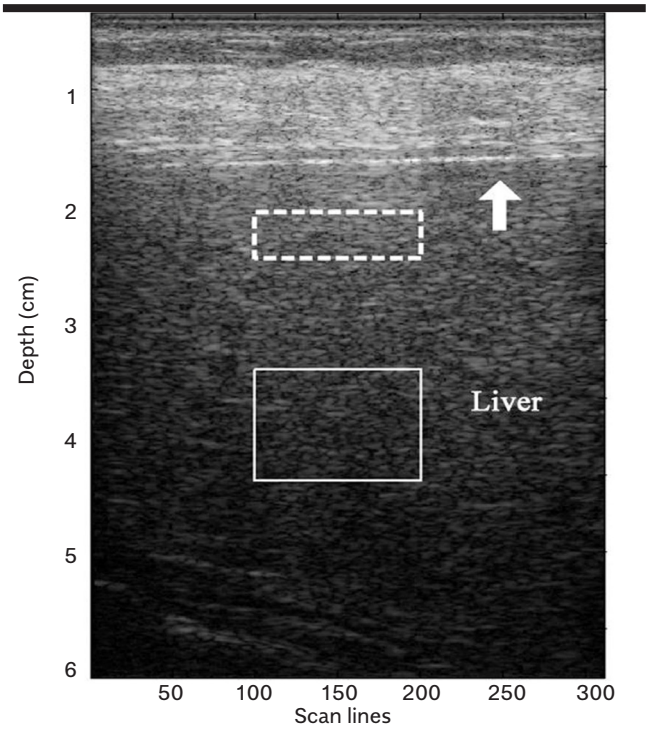

Figure 1. The schematic diagram of W-Ac measurement method in vivo. The dashed box represents the reference region, the solid box represents the ROI, and the high-echo line above the arrow indicates the liver capsule. W-Ac, wave-number domain attenuation coefficient.

Table 1. Correlation between W-Ac and METAVIR score in patients with hepatitis B virus liver disease (n=46).

Variables	F0 (n=12)	F1 (n=13)	F2 (n=10)	F3 (n=7)	F4 (n=4)	p
W-Ac (dB.mm)	0.08662±0.0213	0.11641±0.0265	0.14106±0.0380	0.18426±0.0129	0.18113±0.0142	<0.001

W-Ac: wave-number domain attenuation coefficient.

It is assumed that *m* represents the number of scan lines in the reference region. Based on the fast Fourier transform, the wave-number spectrum of the m^{th} post-beamforming signal $p_r(z, m)$ from the reference region and $p_{roi}(z, m)$ from the ROI are respectively expressed as:

$$\begin{cases} P_r(k,m) = F\ (p_r(z,m)) \\ P_{roi}(k,m) = F\ (p_{roi}(z,m)) \end{cases} \quad (1)$$

where *k* is the wave number, *z* represents the imaging depth, and *m* denotes the m^{th} scan line. Following the ultrasound propagation in the liver tissues between the reference region and ROI, the wave-number domain attenuation was determined as follows:

$$A(k,m) = 20[\log_{10} P_r(k,m) - \log_{10} P_{roi}(k,m)] \quad (2)$$

Also, W-Ac at the m^{th} scan line, $w(m)$, is the slope of the regression line with linear least squares. Consequently, for the whole ROI region, W-Ac can be expressed as:

$$W\text{-}Ac = \frac{1}{M}\sum_{m=1}^{M} w(m) \quad (3)$$

In this method, the post-beamforming signal from the near-field liver tissue was selected as the reference signal to calculate W-Ac of liver parenchyma, which can eliminate the effects of inhomogeneous tissues outside the liver. In addition, we selected an equivalent distance between the reference region and ROI in all experiments to measure W-Ac. Considering the differences in the W-Ac of every liver fibrosis stage, this method could be used to evaluate the liver fibrosis stage.

Liver Biopsy

All the participants underwent liver biopsy at the same site under ultrasound guidance. A 1-second needle biopsy of the liver was performed by one expert physician. According to the METAVIR scoring system (28), METAVIR scores (F0–4) were determined after the histopathological examination of liver biopsies. F1 and F2 were defined as early fibrosis and F3 and F4 were defined as late fibrosis.

Data Collection

Baseline data including the age, sex, and HBV-related liver disease course were recorded.

Statistical Analysis

Statistical analysis was performed using the Statistical Packages for the Social Sciences (SPSS) version 15.0 (SPSS Inc., Chicago, IL, USA). Data related to 5 stages of liver fibrosis are expressed as mean±standard deviation. Differences between the 5 groups and differences between F0, F1–2, and F3–4 stages were evaluated by analysis of variance (ANOVA), whereas comparisons between any 2 stages of fibrosis were made using the least significant difference *t*-test. The F0 and F1–4 groups (normal and fibrotic groups) were also compared using Student *t*-test. In addition, the Spearman's correlation coefficient test was used to determine the correlation between W-Ac and the METAVIR scale. ROC curves analyzed the sensitivity and specificity of the W-Ac method to test whether the liver had fibrosis or not. Statistical significance was set at p<0.05.

RESULTS

Baseline data

A total of 46 participants were enrolled in this study (27 males and 19 females; age, mean42.3years, range [22–60] years) with HBV-related liver disease (disease course, mean 8.2 years,range[5–20] years). The post-beamforming and liver biopsy data were successfully collected from all participants. Histopathological examination according to the METAVIR scoring system showed stage F0 fibrosis in 12 patients, F1 in 13 patients, F2 in 10 patients, F3 in 7 patients, and F4 in 4 patients (Table 1). The results showed that W-Ac increased as the severity of liver fibrosis increased up to stage F3, although there were overlaps between the groups (Figure 2). There was a significant correlation between W-Ac and METAVIR score (r=0.795, p<0.001).

Study of 5 stages of liver fibrosis

The ANOVA results showed that the differences between F0 and F4 stages were significant (p<0.001, Table 1). The post-hoc analysis also showed significant differences between any 2 stages of fibrosis (p<0.05), except for stages F3 and F4.

Differentiation of normal liver (F0) and fibrotic liver (F1–4)

To evaluate whether our method could distinguish fibrotic livers from normal ones, we divided the 46 participants

into 2 groups according to the METAVIR scale: normal (F0) and fibrotic (F1–4) groups. The results of the Student *t*-test showed that W-Ac differed significantly between these groups (p<0.001) (Table 2).

Study of normal, early fibrosis (F1–2), and late fibrosis (F3–4) stages

Complete recovery may be achieved in the early stages of liver fibrosis if appropriate medications are prescribed. So, we evaluated the differences in the early fibrosis stages (F1–2) from other stages (F0 and F3–4). The results indicated significant differences among the 3 groups (p<0.001, Table 3), and post-hoc analysis showed differences between the normal group (F0), the early fibrosis group (F1–2), and the late fibrosis group (F3–4) (all p<0.05).

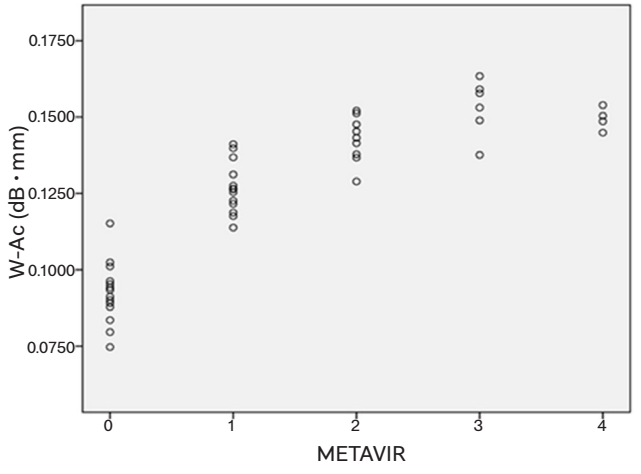

Figure 2. W-Ac and METAVIR score for each with hepatitis B virus liver disease (n=46; r=0.795, p<0.001). W-Ac, wave-number domain attenuation coefficient.

Table 2. Comparison of W-Ac between normal liver and liver fibrosis groups.

Variables	Normal group (F0) (n=12)	Fibrotic group (F1–4) (n=34)	p
W-Ac (dB.mm)	0.08662±0.0213	0.14524±0.0386	<0.001

W-Ac: wave-number domain attenuation coefficient.

ROC curve test of the method

The ROC curve analysis showed that using the W-Ac method to test for the presence of fibrosis had an area under the curve (AUC) of 0.890, and at a cut-off of 0.12153, sensitivity was 0.706 and specificity was 0.830 (Figure 3).

DISCUSSION

The aim of this study was to investigate the feasibility of using the W-Ac values obtained from ultrasound in non-invasive staging of liver fibrosis in patients with liver disease. Therefore, patients with HBV infection were prospectively included in this study, and their ultrasound imaging results were analyzed to produce the W-Ac value that was compared with liver biopsy results. The results showed that there were differences in W-Ac values between F0 and F4 stages and between any 2 stages of fibrosis, except for stages F3 and F4. There was a significant correlation between W-Ac and METAVIR score. W-Ac differed between non-fibrosis (F0) and fibrosis (F1–F4) groups and in between normal (F0), early fibrosis (F1–2), and late fibrosis groups (F3–4). The ROC curve that tested the ability of the method to distinguish between liver fibrosis or not had an AUC of 0.890, and at a cut-off of 0.12153, sensitivity was 0.706 and specificity was 0.83. Therefore, these results suggest that W-Ac allowed non-invasive assessment of liver fibrosis in clinical practice.

Many researchers have focused on developing non-invasive methods for the assessment of liver fibrosis. Ultrasound is widely accepted by patients and clinicians because of its relative accuracy, greater compliance, and lower cost. So, many non-invasive methods include novel ultrasound analysis techniques, such as acoustic structure quantification (29,30) and echo amplitude distribution (31,32), which have shown some promise in preliminary studies in staging liver fibrosis. However, the

Table 3. Comparison of W-Ac in the normal, early fibrosis, and late fibrosis groups.

Variables	Normal group (F0) (n=12)	Early fibrosis group (F1–2) (n=23)	Late fibrosis group (F3–4) (n=11)	p
W-Ac (dB.mm)	0.08662±0.0213	0.12712±0.0332[a]	0.18312±0.0128[ab]	<0.001

W-Ac: wave-number domain attenuation coefficient.
[a]p<0.05 compared with normal group; [b]p<0.05 compared with early fibrosis group.

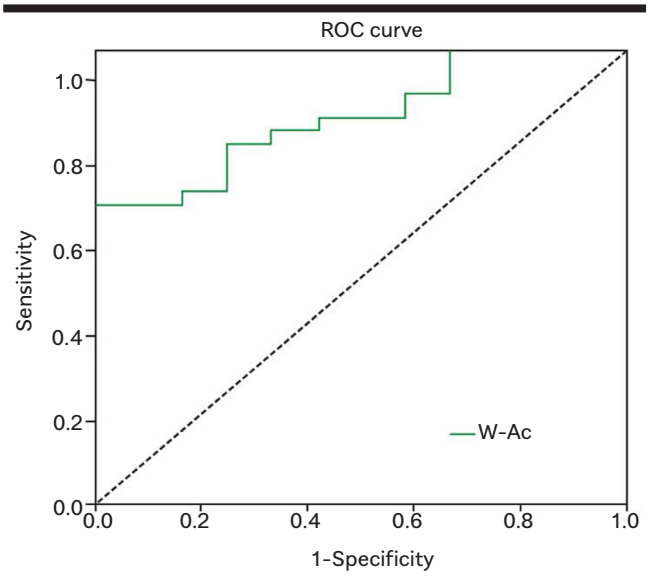

Figure 3. ROC curve for determining whether there was liver fibrosis or not using the W-Ac method. The AUC was 0.890, and at a cut-off of 0.12153, sensitivity was 0.706 and specificity was 0.83. AUC, area under the curve; ROC, receiver operating characteristic; W-Ac, wave-number domain attenuation coefficient.

most common ultrasound methods for assessing liver fibrosis involve elastography techniques (16–22). Elastography only assesses stiffness, and although liver stiffness is strongly correlated with fibrosis stage, elastography tends to have a high degree of accuracy in the diagnosis of advanced liver fibrosis but not the diagnosis of early liver fibrosis (33). Therefore, this study used a new method based on W-Ac as an alternative approach to ultrasound analysis based on studies that have shown that acoustic attenuation composition is closely related to liver fibrosis stage in vitro (24–27). The results of this study suggest that W-Ac was useful in staging liver fibrosis.

The most prominent advantage of the method used in this study is that it can eliminate the effects of inhomogeneous tissues outside the liver and account for differences between body compositions in different patients to accurately measure the actual attenuation of liver tissues. By setting an equivalent distance between the reference region and ROI for all experiments, the calculated W-Ac should indicate the attenuation of different liver tissues and the liver fibrosis stage.

Generally, a normal liver parenchyma consists of uniform microstructures, and the acoustic impedance varies slightly; therefore, a low W-Ac was found in the normal group. During liver fibrosis, fibrotic structures and nodules develop, leading to poor uniformity and a relatively high degree of variance in the acoustic impedance. Therefore, attenuation of ultrasound signals through liver tissues increased in the F0–3 groups, whereas a downward trend was reported in the F4 group, which might be caused by the similar acoustic characteristics of new liver regeneration nodules and normal liver tissues.

Additionally, we divided 46 participants into 2 groups according to the METAVIR score: the normal group (F0) and the fibrosis group (F1–4). The results showed that W-Ac differs significantly between these 2 groups; accordingly, W-Ac might be effective in the differential diagnosis of fibrosis.

It is well established that complete recovery can be achieved in the early stages of liver fibrosis if appropriate medications are prescribed. In this study, we divided all participants into 3 groups according to the METAVIR score: normal group (F0), early fibrotic group (F1–2), and late fibrotic group (F3–4). The results showed significant differences between each 2 groups. Therefore, W-Ac is applicable for the differential diagnosis of early and late fibrosis stages and can be beneficial in the follow-up of patients with chronic HBV.

This pilot study has some limitations, such as the small sample size and lack of inflammatory grading for each of the patients. A more detailed analysis of the ability of W-Ac to grade liver fibrosis would be possible with results from more patients. It would also be helpful to compare these results to established transient elastography methods. The relationship between W-Ac and liver fibrosis degree needs to be confirmed in larger prospective multicenter studies.

In conclusion, this study presents a new non-invasive method for measuring the attenuation of ultrasound signals based on post-beamforming data to evaluate the stage of liver fibrosis. W-Ac increased with the progression of liver fibrosis to stage F3. W-Ac was able to differentiate between non-fibrosis (F0), early fibrosis (F1–2), and late fibrosis (F3–4) groups.

Ethics Committee Approval: This study was approved by the Institutional Ethics Committee of the First Affiliated Hospital of Anhui Medical University (Decision No:AF/SC-08/02.0,Decision Date:12.12.2016).

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – D.H., C.Z.; Design – D.H., C.Z.; Supervision – C.Z., Q.X.; Resource – Q.X.; Materials – Q.X.; Data Collection and/or Processing – D.H., W.Q.; Analysis and/or Interpretation – D.H., W.Q.; Literature Search – D.H., W.Q.; Writing – D.H., W.Q.; Critical Reviews – D.H., W.Q.

Conflict of Interest: The authors have no conflict of interest to declare.

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