

Original Article

The diagnostic value comparison of real-time elastography and sound velocity tissue quantification for detection of chronic hepatitis B infection induced liver fibrosis

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Abstract: Aim: This study is to compare the diagnostic value of real-time elastography (RTE) and sound velocity tissue quantification (SVQ) for detection of chronic hepatitis B infection induced liver fibrosis. Methods: In this study, 79 patients with chronic hepatitis B infection induced liver fibrosis and 110 healthy people underwent SVQ and RTE, ROC curve was generated using pathology as gold standard for diagnosis. Results: Using liver fibrosis and normal liver sound velocity as reference, the sensitivity, specificity, positive predictive value and negative predictive value of SVQ for liver fibrosis cases were 81%, 84%, 82%, 88%, and 75% respectively. The sensitivity, specificity, positive predictive value and negative predictive values of RTE were 94%, 81%, 89%, 88% and 90%, respectively. Conclusion: SVQ and RTE are both of great diagnostic value for hepatitis B infection induced liver fibrosis.

Keywords: Real-time elastography, sound velocity tissue quantification, chronic hepatitis B infection, liver fibrosis

Introduction

Hepatitis B virus (HBV) infection is the world's most common type of liver infection that threatens human health globally [1]. China is one of the countries with the highest prevalence of HBV infection [2]. HBV is a viral infection that attacks the liver and can cause both acute and chronic disease, such as liver fibrosis, cirrhosis, ascites and even liver cancer [3]. Liver fibrosis is a pathological process that caused by various chronic liver injuries, and liver fibrosis would progress to cirrhosis without intervention [4]. For the above reasons, the diagnosis and detection of liver fibrosis is particularly important.

There is no significant difference between early fibrosis and normal tissue on conventional ultrasound, thus it can only detect cirrhosis when in the final stage, in which no treatment can reverse liver fibrosis [5]. It is shown that though there is no significant morphology change in the early stage of cirrhosis, the tissue elasticity has already changed, and early detec-

tion of this change can diagnose early liver fibrosis [6].

Currently, the gold standard for liver fibrosis diagnosis is liver biopsy, which is seldom accepted by the majority of patients due to its potential risks and complications, and biopsy cannot be used for the dynamic monitor of fibrosis staging [7]. Therefore, non-invasive fibrosis evaluation method is being developed in recent years. Real-time elastography (RTE) is widely applied in superficial organ detection, and its use in liver fibrosis diagnosis has been explored lately [8, 9]. Sound velocity tissue quantification (SVQ) is a new kind of ultrasound imaging technology that has been used for tissue elasticity evaluation by tracking sound velocity [10]. In this study, SVQ and RTE were compared for the detection of liver fibrosis.

Methods

Subjects

The 79 patients with HBV infection and 110 healthy people were recruited by Department

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of Gastroenterology, Zhengzhou University Second Hospital from January 2013 to March 2014. Healthy people were considered as control group, including 55 males and 55 females with mean age of 37.1 ± 12.8 years (ranging from 22 to 78 years). All people in control group had no previous liver disease, and ultrasound and laboratory tests of liver function showed negative or within normal range. In HBV patient group, all patients were diagnosed with fibrosis by biopsy. There were 51 males and 28 females, with mean age of 38.7 ± 14.2 years, ranging from 23 to 79 years. Prior written and informed consent were obtained from every patient's family and the study was approved by the ethics review board of The Second Associated Hospital of Zhengzhou University.

HE staining

The 79 patients with HBV infection underwent liver biopsy with ultrasound guidance. The biopsy tissue was fixed by 10% formaldehyde and was embedded by paraffin. HE staining was performed according to routine procedure. Its pathology was assessed by experienced pathologists.

Equipment

Z.one color Doppler ultrasound (ZONARE Co., Ltd., California, US) and C5-2 probes were used with probe frequency of 2-5 MHz. Its sound velocity (SV) feature can detect the tissue SV or zone speed index (ZSI, unit: m/s) in tissue of interest. Hitachi HI VISION Preirus (Hitachi, Ltd., Tokyo, Japan) color Doppler ultrasound and linear array probe L52 was used with frequency of 3-7 MHz and RTE features.

Procedures

Subjects were in supine position with right arm above the head to fully expose the abdomen and extend intercostal space. The 5-8 intercostal axillary spaces were chosen for detection. Two-dimensional gray-scale ultrasonography was performed first, and SVQ proceeded as following. The subcapsular 1 cm of liver was set as region of interest (ROI) with a fixed size of 35×35 mm to avoid large intrahepatic duct. The instrument would automatically calculate the ZSI (zone speed index) value. The value was measured 6 times in the same position for average, and the SV of ROI was calculated as $SV = (1540 + ZSI)$ m/s. Then subjects underwent RTE as following: ROI was set as subcapsular 1 cm, and liver tissue with

thickness of 3.0 cm and area of 2.5×2.5 cm² was used, to avoid the large blood vessels and rib shadows. The sampling area was the same area that underwent liver biopsy. The elastography was taken as patient's own heart beat. The pressure-strain curve represents the image and frequency of liver in light of heart beats image, with real-time two-dimensional figure and elasticity figure. The color-coded elasticity figure represented the liver fibrosis distribution [3, 5, 11]. When the stress-strain curve was stable for at least five troughs, trough figure with the largest area was taken and analyzed by mean (MEAN), standard deviation (SD), blue area (%AREA), complicatedness (COMP), kurtosis (KURT), skewness (SKEW), contrast (CONT), equalization (ENT), IDM, ASM, correlation (CORR). The value was measured for 5 times in the same position for average, and Japanese hepatitis C fibrosis formula [6] was used for liver fibrosis index (LF Index). $LF\ Index = 0.008897 * MEAN - 0.023 * \%AREA + 0.025 - 3 * COMP + 0.775 * SKEW - 0.281 * KURT + 2.08 * ENT + 3.04 * IDM + 40.0 * ASM - 5.54$.

Statistical analysis

Statistical Package for the Social Sciences 20.0 was used for statistical analysis. Liver biopsy was used as gold standard to respectively analyze the sensitivity, specificity and accuracy of SVQ and RTE for diagnosis of liver fibrosis. The accuracy comparison between groups used Mc-Nemar chi-square test. The ROC (receiver operating characteristic) curve was drawn with positive pathology diagnosis as reference. Z test was used for ROC curve. $P < 0.05$ was considered statistically significant.

Results

Liver fibrosis staging

To determine the liver fibrosis staging, pathology was performed. The liver fibrosis staging was defined as [12]: stage 0 (S0), no fibrosis; stage 1 (S1), periportal fibrosis limited in perisinusoidal and lobular; stage 2 (S2), perivascular fibrosis with periportal fibrous septa formation and lobular structure retention; stage 3 (S3), fibrous septa with lobular structure derangement, without cirrhosis; stage 4 (S4), early cirrhosis or confirmed cirrhosis. Of the 79 patients with chronic HBV infection, there were 32 patients of S0, 18 patients of S1, 11 patients of S2, 6 patients of S3, and 12 patients of S4. In conclusion, there were 47 positive cases, and 32

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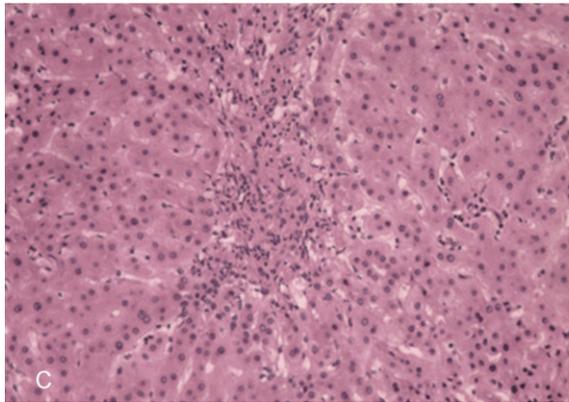
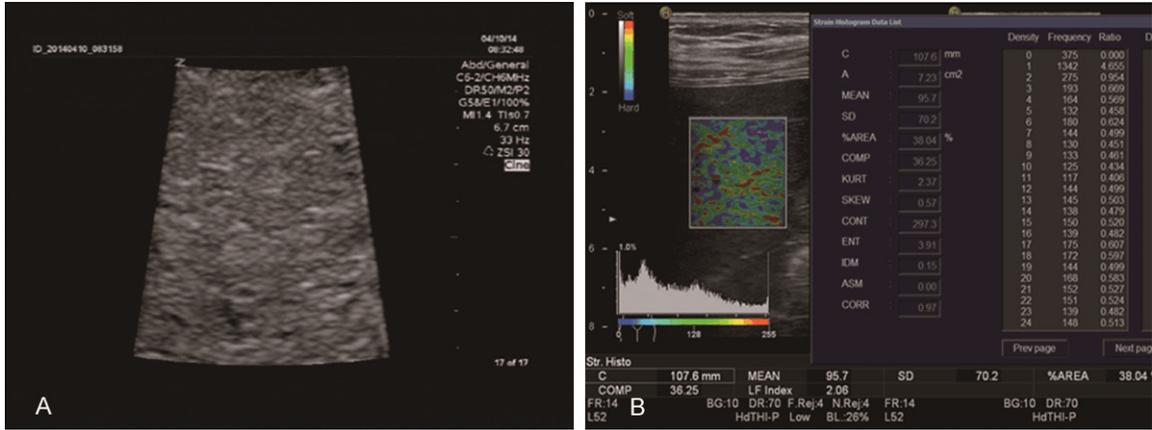


Figure 1. Images of fibrosis S2. A. The diagram of ZSI measurement in fibrosis S2. B. The elastography in fibrosis S2. C. The pathology in fibrosis S2.

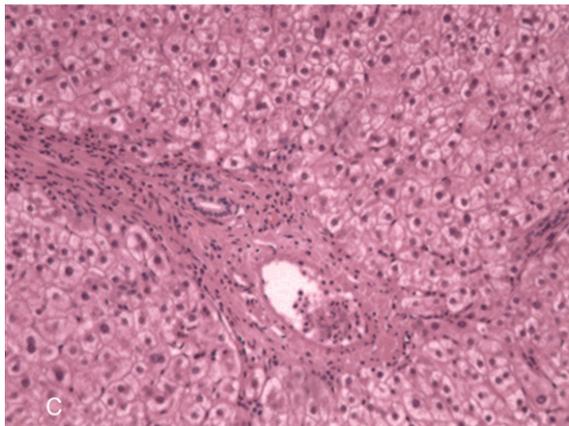
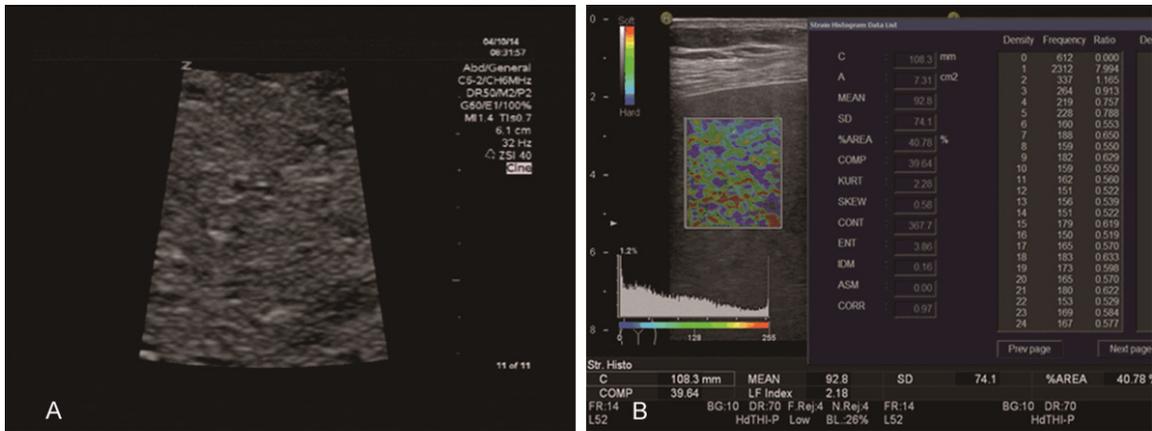


Figure 2. Images of fibrosis S3. A. The diagram of ZSI measurement in fibrosis S3. B. The elastography in fibrosis S3. C. The pathology in fibrosis S3.

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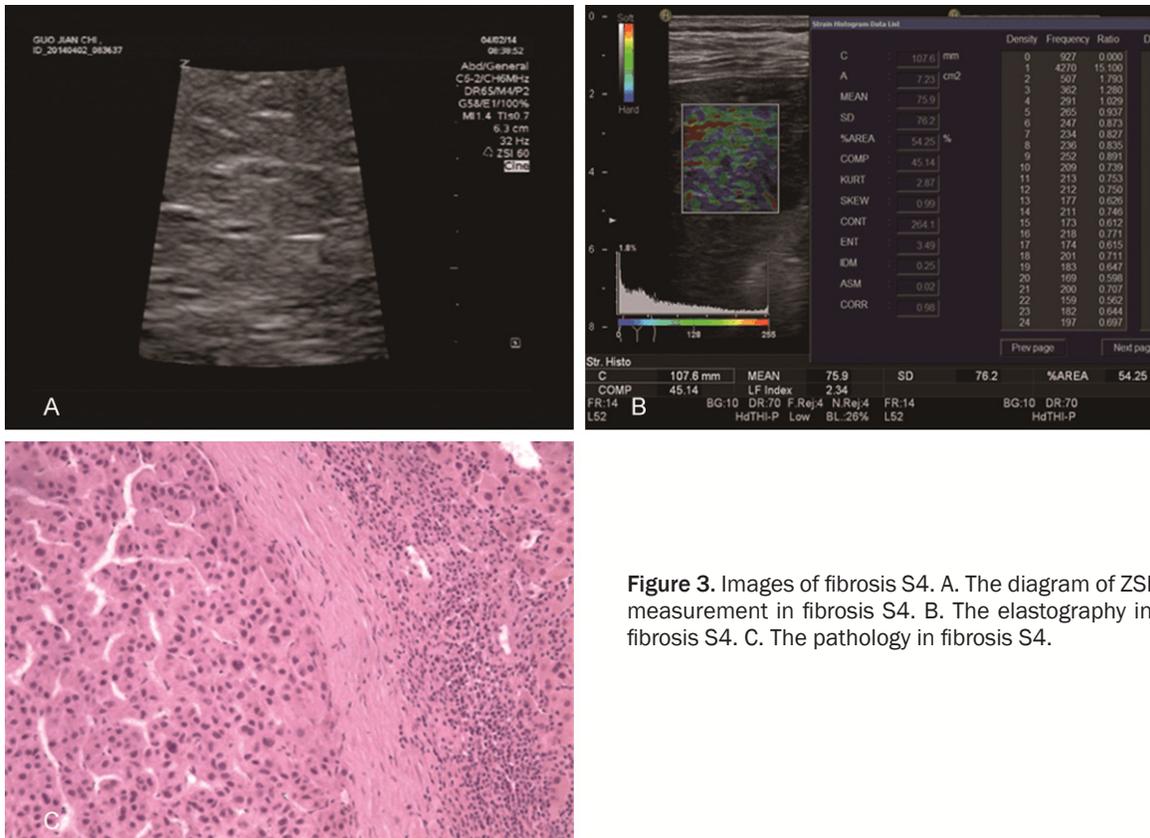


Figure 3. Images of fibrosis S4. A. The diagram of ZSI measurement in fibrosis S4. B. The elastography in fibrosis S4. C. The pathology in fibrosis S4.

Table 1. Comparison of SVQ and pathology of liver cirrhosis diagnosis

Diagnostic method	Sensitivity	Specificity	Accuracy	Positive predictive value	Negative predictive value
SVQ	81% (38/47)	84% (27/32)	82% (65/79)	88 % (38/43)	75% (27/36)
Pathology	100% (47/47)	100% (32/32)	100% (79/79)	100% (43/43)	100% (36/36)
P value	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05

SVQ: Sound velocity tissue quantification.

negative cases (Figures 1-3). Figure 1 showed the pathology of S2 and its corresponding ZSI and LF Index. Figure 2 showed the pathology of S3 and its corresponding ZSI and LF Index. Figure 3 showed the pathology of S4 and its corresponding ZSI and LF Index. From the figures, it showed that the more advanced of liver fibrosis, the increased ZSI and LF Index. Because of the late detection of liver fibrosis, there is no corresponding pathology in this study.

ROC curve

To compare the diagnostic efficiency, ROC curve was plotted with pathology diagnosis as reference. The area under ROC (AUC) of SVQ

was 0.894 (95% CI: 0.826-0.963) and the maximum Youden was 0.653, with corresponding SV of 1575 m/s. At this point, the sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of SVQ was 81% (38/47), 84% (27/32), 82% (65/79), 88% (38/43), and 75% (27/36), as shown in Table 1. The ROC curve showed that SVQ was of diagnostic value and the possibility of fibrosis was increasing as SV increased, with statistical significance ($P < 0.05$).

The AUC of RTE was 0.947 (95% CI: 0.872-0.985) and the maximum Youden was 0.779, with corresponding IF Index of 1.92. At this point, the sensitivity, specificity, accuracy, positive predictive value, and negative predictive

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Table 2. Comparison of RTE and pathology of liver cirrhosis diagnosis

Diagnostic method	Sensitivity	Specificity	Accuracy	Positive predictive value	Negative predictive value
RTE	94% (44/47)	81% (26/32)	89% (70/79)	88% (44/50)	90% (26/29)
Pathology	100% (47/47)	100% (32/32)	100% (79/79)	100% (50/50)	100% (29/29)
P value	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05

RTE: Real-time elastography.

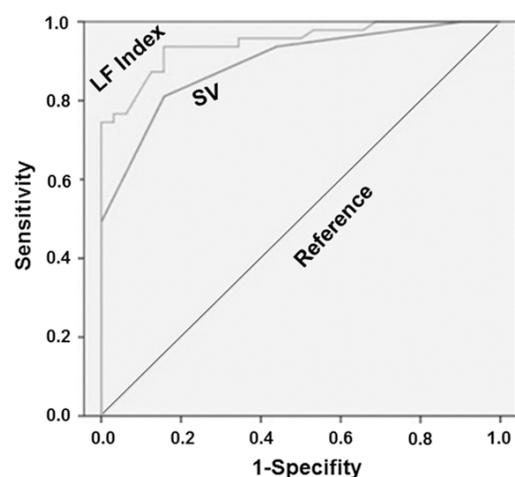


Figure 4. The ROC curve using positive pathology as reference.

Table 3. The specificity, accuracy, and sensitivity comparison between RTE and SVQ

Diagnostic method	Specificity	Accuracy	Sensitivity
RTE	81%	89%	94%
SVQ	84%	82%	81%
P value	1.0	0.065	0.041

SVQ: Sound velocity tissue quantification. RTE: Real-time elastography.

value of RTE was 94% (44/47), 81% (26/32), 89% (70/79), 88% (44/50), 90% (26/29), as shown in **Table 2**. The ROC curve showed that the RTE was of diagnostic value and the possibility of fibrosis was increasing as IF Index increased, with statistical significance ($P < 0.05$).

Comparison between SVQ and RTE

To compare the diagnostic value of SVQ and RTE, ROC curve was drawn using pathology diagnosis. The AUC of SVQ and RTE was 0.894 and 0.947, with no significance ($P = 0.116$), as shown in **Figure 4**. There were no significant dif-

ferences of diagnostic specificity ($P = 1.0$) and accuracy ($P = 0.065$) between the groups. The sensitivity of RTE was higher than SVQ with significance ($P = 0.041$), as shown in **Table 3**.

Discussion

Liver fibrosis is the early stage of cirrhosis, and it is resulted from all kinds of chronic liver diseases. Liver fibrosis can be reversed but advanced cirrhosis cannot [13]. Therefore, early diagnosis and early treatment of liver fibrosis is of great importance for disease deterioration. In recent years, improved RTE can detect the elasticity signal of ROI by external forces through color-coded image to measure tissue cirrhosis [14]. The quantitative analysis of RTE, differed from the conventional ultrasound, relied on heart beat related liver tissue movement. With indicator analysis and fibrosis index calculations in ROI, the staging and extend of liver fibrosis can be analyzed.

In this study, RTE was applied to differentiate normal liver tissue and liver fibrosis to improve its early diagnosis, with diagnostic sensitivity, specificity and accuracy of 94%, 81% and 89% respectively. It showed the high diagnostic value of RTE, and it can be used as supplement for liver fibrosis diagnosis [15].

SVQ measures the tissue SV to detect lesion elasticity [16]. The human tissue SV depends mainly on tissue density and elasticity, thus SV will change when chronic HBV infection damaged the tissue [17]. Conventional ultrasound assumed SV of 1540 m/s, while the SV differs in different tissue of the same people [18]. SV changes as tissue type and elasticity change [19]. Therefore, SV can represent tissue elasticity, and SVQ captures the tissue velocity index and its difference with 1540 m/s. SVQ scans the images of the same section with different SV, and then analyze the lateral resolution and signal [18]. The image with best resolution and maximum signal was identified, and the corre-

sponding SV was the average velocity. In vitro experiments it have shown that the detected SV was similar to SV in tissue, thus can indirectly evaluate tissue fibrosis based on changes of liver tissue pathology [18, 20]. In this study, the sensitivity, specificity and accuracy of SVQ was 81%, 82% and 88% respectively, indicating its high diagnostic value for liver fibrosis.

In this study, there was no difference of specificity and accuracy between SVQ and RTE, but the sensitivity of RTE was higher than SVQ ($P = 0.041$), indicating higher true positive rate of RTE. The AUC of the two methods was both greater than 0.8, indicating the high diagnosis value of SVQ for early diagnosis of liver fibrosis.

In this study, there were 3 cases of negative RTE and positive pathology, and 6 cases of positive RTE and negative pathology. The above different evaluation can be resulted from the small biopsy area compared with elasticity ROI (1:50,000) and the uneven distribution of liver fibrosis. In practice, it was of great importance to avoid shadows of thick blood vessels and ribs, as well as liver in deep regions for its difficult imaging. In addition, RTE was limited in diagnosis for patients with severe obesity, severe liver atrophy and intercostal space stenosis [21].

In this study, there were 9 cases of negative SVQ and positive pathology, and 5 cases of positive SVQ and negative pathology. The above difference can be resulted from uneven distribution of liver fibrosis, thus the fibrosis of ROI cannot represent the whole liver. In addition, SVQ is limited in representing sampling depth, and eliminating external sound influences of ZSI value.

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Disclosure of conflict of interest

None.

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