Comprehensive tools for the evaluation of diffuse liver disease

Foreword

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Liver disease is a huge global burden which leads to heavy financial burden for the patients and healthcare systems, along with premature loss of productivity due to patients' suffering. Early detection is the key for effective liver disease management and improvement in the patient's quality of life.

The Aplio™ i-series diagnostic ultrasound system incorporates the latest generation architecture and advanced transducer technology to deliver a new level of image quality. The newly developed liver tools aim to support clinicians to evaluate diffuse liver disease easier and faster.

Staging of diffuse liver disease is fundamental for risk quantification before a patient suffers from unrecoverable end-stage liver disease such as cirrhosis and HCC. On the Aplio i-series, three innovative applications are imbedded for diagnosing diffuse liver disease by assessing liver characteristics: Shear Wave Elastography (SWE) for liver stiffness, Shear Wave Dispersion (SWD) for liver viscosity, and Attenuation Imaging (ATI) for attenuation in liver.

Shear Wave Elastography is used for quantifying liver stiffness and is currently one of the advanced tools that has received a growing clinical acceptance for analyzing fibrosis. Nevertheless, it is commonly known that SWE has its limitations for the evaluation of steatosis and inflammation. Shear Wave Dispersion is a newly developed tool based on shear wave technology which analyzes the frequency dispersion properties in liver for assessing liver viscosity. In addition, Attenuation Imaging is another unique tool that quantifies the attenuation coefficient in the liver tissue to determine the degree of steatosis.

Shear Wave Elastography, Shear Wave Dispersion, and Attenuation Imaging are incorporated into the Liver Package on Aplio i-series to offer clinicians additional information on liver characteristics during diffuse liver disease assessment. The Liver Package allows clinicians to gather more information about liver tissue characteristics and guides them through earlier detection, accurate and precise staging, along with effective therapy monitoring and post-treatment follow-up. Liver ultrasound can therefore become a reliable, non-invasive, and cost-effective method to reduce unnecessary invasive liver biopsies.

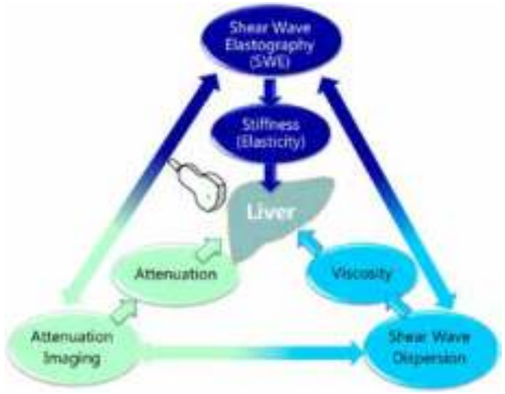

Figure 1 The Liver Package on the Aplio i-series

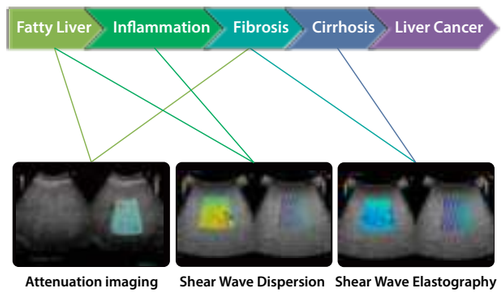

Figure 2 Evaluation of diffuse liver disease with the Liver Package

Diagnosis of liver fibrosis using Shear Wave Elastography

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Introduction

Liver ultrasound is one of the state-of-the-art methods for diagnosing diffuse liver disease. Cirrhosis is a chronic liver disease in which normal liver tissue is replaced by scar tissue through the process of fibrosis, increasing liver stiffness. Major causes of cirrhosis include hepatitis B (HBV), hepatitis C (HCV), alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD). Hepatocellular carcinoma (HCC) is one of the most common complications for patients with cirrhosis.

Clinically, it is important to determine the risk of developing liver cancer and the need for antiviral treatment. The increasing incidence of HCC in the aging population with HCV is a major issue. Recently, the global trend for HCV treatment is the administration of the direct acting antiviral agent (DAAs). [1] As a result, early detection, accurate staging and treatment evaluation of fibrosis are essential for optimizing patient management.

Biopsy is considered to be the gold standard for fibrosis diagnosis, even as the incidence of liver biopsies being performed has reduced due to the invasiveness and cost. It is also reported that the sampling variability can affect the accuracy of liver biopsy. [2] Blood chemistry examinations are also employed, however their diagnostic accuracy is not particularly high. Observing speckle patterns in B-mode images is one of the approaches for staging fibrosis, however, the differentiation between fibrosis stages F1 and F2 is indeed challenging. There have been attempts to perform tissue diagnosis using morphology of the liver surface, however it provides no additional information above the estimation of liver stiffness by manual palpation.

Shear Wave Elastography is an innovative application to assess hepatic fibrosis and stiffness, and is increasingly employed in the clinical setting. According to the EASL-ALEH Clinical Practice Guidelines, for patients with confirmed etiology of cirrhosis SWE is recommended in order to avoid unnecessary biopsy procedures. [3] With the novel iBeam architecture in the Aplio i-series, SWE images are acquired with better sensitivity and fewer artifacts.

In this paper, the usefulness of SWE in diagnosing liver stiffness is evaluated and SWE results acquired during clinical evaluation are compared with other state-of-the-art techniques for analyzing diagnostic accuracy.

Technical background of SWE

Shear Wave Elastography (SWE) measures the velocity of shear wave propagation within the liver for liver stiffness quantification.

The concept of SWE can be explained using an earthquake as an example. In an earthquake, energy released from the fault movement generates seismic waves. A primary wave (P-wave) is generated followed by a secondary seismic wave (S-wave), which travels much slower than the P-wave. The S-wave (shear wave) vibrates the ground perpendicular to the direction of movement. S-waves travel faster in hard matter than soft matter as their particles are more condensed. In the case of SWE, a push pulse emitting from a transducer is similar to the fault movement, generating an ultrasound wave which deforms the liver tissue (Figure 2a). The shear wave is

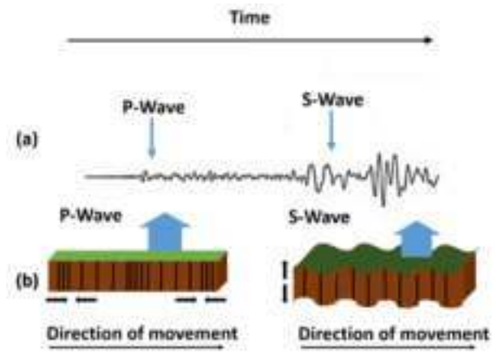


Figure 1 (a) Seismic waves detected on a seismogram at a recording station on the earth surface.
(b) P-wave is the first wave detected followed by the S-wave, a secondary wave which vibrates the ground up and down.

created during the tissue deformation. Similar to the earthquakes S-wave, shear waves transmit perpendicular to the ultrasound wave (Figure 2b). In the human body, the shear waves transmit slowly at a velocity of approximately 1 m/s to 10 m/s, making them detectable with a diagnostic ultrasound system. In addition, the propagation velocity differs significantly depending on the tissue stiffness. If a lesion such as a tumor is present in the tissue, the shear wave velocity in that area differs from that in the surrounding tissue. If the lesion is stiffer, the shear waves propagate faster (Figure 2c), and vice versa. The propagating shear waves are detected using tracking pulses (Figure 2d).

At each data point, the time at which the shear waves arrive is plotted (Figure 2e). By plotting time against propagation of the shear wave, a trace of shear wave propagation within the liver is obtained (Figure 2f).

In uniform tissue, the shear wave velocity is constant and the tracing slope is uniform. In inhomogeneous tissue, the tracing slope varies with the shear wave velocity detected. For example, if a stiff tumor is present in the liver, the area with a higher shear wave velocity (stiffer area) is displayed in red (Figure 2g).

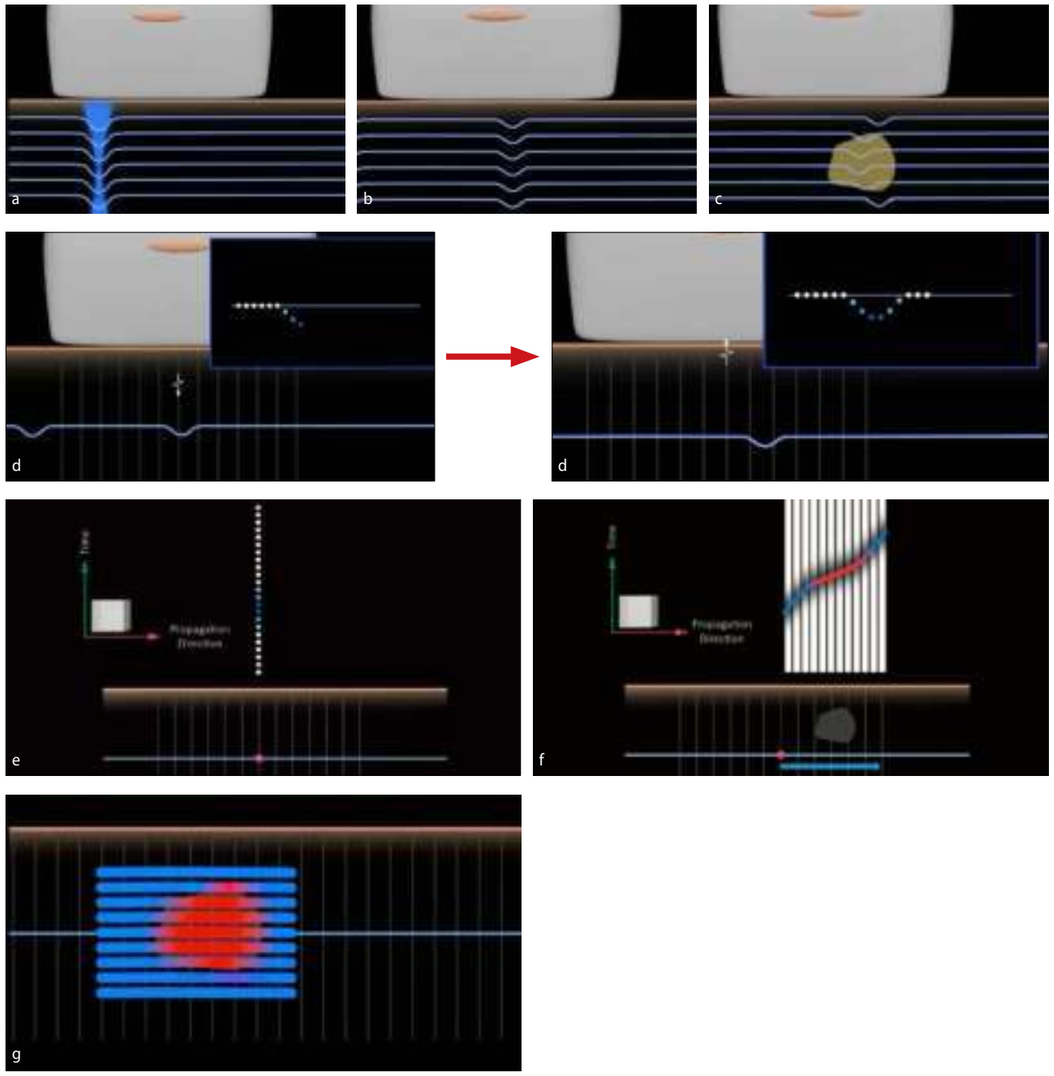


Figure 2 Technical background of SWE

One of the major features of Aplio SWE is that clinicians are able to select the continuous scan (real-time scan) or one-shot scan which has a higher sensitivity. One shot scan is preferred for SWE acquisition and continuous scan is useful for evaluating areas which experience motion artifacts. At our institution, we select one-shot scan in order to obtain higher image quality. Another major feature of Aplio SWE is Smart Maps, allowing clinicians to visualize tissue characteristics or propagation of the shear wave. In our institute, we use the Speed Map (m/s), Elasticity Map (kPa) and Propagation Map (arrival time contour) to evaluate liver stiffness (Figure 3).

Reliability of SWE acquisition

The Propagation Map (arrival time contour) serves as a reliability indicator for SWE data acquisition in order to increase diagnostic accuracy and intra/inter-operator reliability. The Propagation Map displays the wavefronts of the shear wave at a fixed time interval, showing whether the shear waves propagate smoothly (Figure 4). The distance between the contour lines are wider in stiffer tissues because of a longer time interval (Figure 5). In areas with parallel contour lines, the shear waves propagate smoothly and the reliability of data acquisition is high. In areas where the contour lines are distorted or not in parallel, the reliability of the data acquisition is low. In other words, the reliability of data acquisition can simply be verified by observing the contour lines (Figure 6).

Although color is not mapped in areas where inhomogeneity is overly high, e.g. influence from vessels or acoustic shadowing, shear wave propagation can still be observed clearly in contour display to support SWE acquisition. In addition, the contour display makes it possible to verify the data reliability in deeper regions where attenuation is high. As discussed above, Propagation Map is a very useful tool for verifying the reliability of data acquisition and for selecting optimal positions for shear wave velocity measurement.

In an example of a patient with severe fatty liver and a skinfold thickness of 3 cm, it was still possible to obtain data with verified reliability by determining the area in which the shear waves propagate uniformly using the propagation map and measuring the velocity of shear wave within the area (Figure 7).

Improvement of SWE on the Aplio i-series

The innovative iBeam architecture embedded in the Aplio i-series forms thin slice beams thus significantly elevates the sensitivity in SWE acquisition for more stable results. Shear wave velocity is detected with fewer artifacts and the value can be mapped more precisely on the SWE ROI. Clinicians are now able to obtain SWE data faster and easier during SWE examinations.

In our institute, we have been using the Aplio Platinum

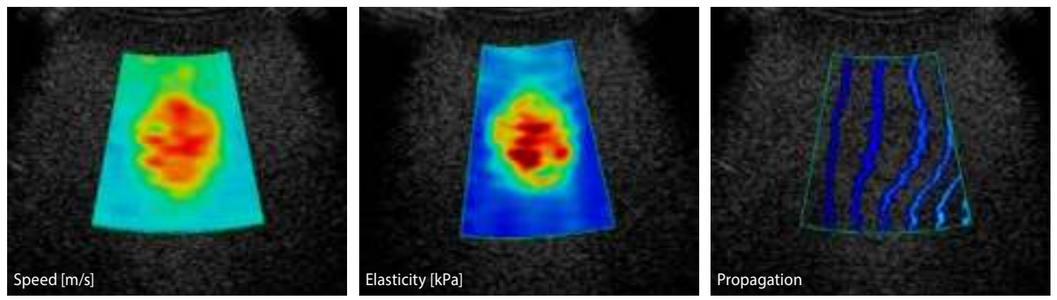


Figure 3 Smart Maps

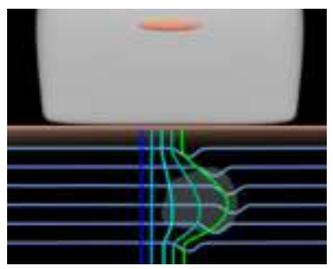


Figure 4 Principle of propagation map

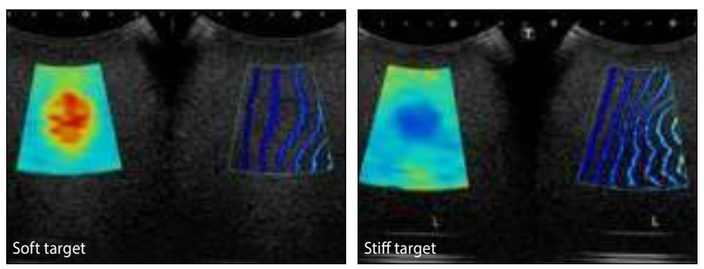


Figure 5 Propagation map on a stiff and soft target

Series, Aplio 500, for SWE evaluation since 2014. We compared the Aplio 500 and Aplio i-series in order to observe the system differences. The correlation coefficient between the systems is 0.96, exhibiting an excellent consistency.

Patients with liver metastasis are often reported with higher values of shear wave velocity. The shear wave velocity in a 50 year-old female with liver metastasis (Figure 8) was calculated using Aplio 500 and Aplio i800. On Aplio i800, a bullseye pattern on the lesion is clearly depicted on the B-mode image. The speed map clearly demonstrated the intralesional stiffness and the propagation map showed that the arrival time contours were more consistent, enabling a better interpretation of SWE acquisition. With the thin slice beam, there are fewer artifacts from structures such as vessels.

Quadrant view (Quad View) for SWE is available on Aplio i-series and allows simultaneous observation of the Speed/Elasticity Map, Propagation Map, Grayscale and Dispersion Map, which is a new application for assessing liver viscosity (Figure 9). The quantification of shear wave speed, shear wave elasticity and dispersion are displayed in Quad View, facilitating diagnostic efficacy as clinicians can perform comprehensive analysis by investigating different tissue characteristics.

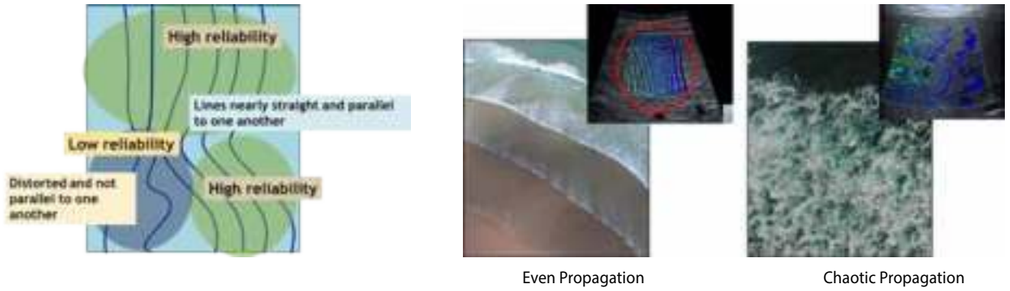
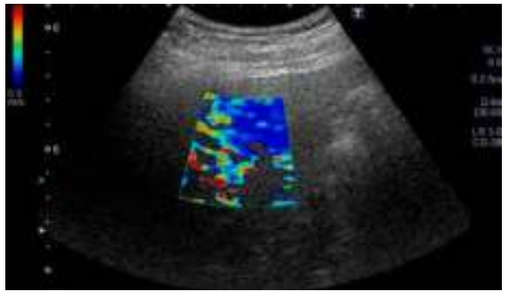


Figure 6 Reliability of propagation display based on the contour lines



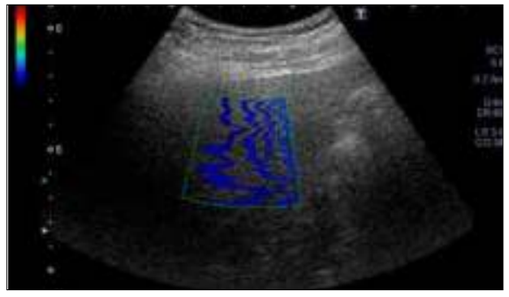


Figure 7 Patient with severe fatty liver. Parallel contour lines are observed in the upper-right part of the image in Propagation Map. The measurement data can be verified to be reliable in such areas.

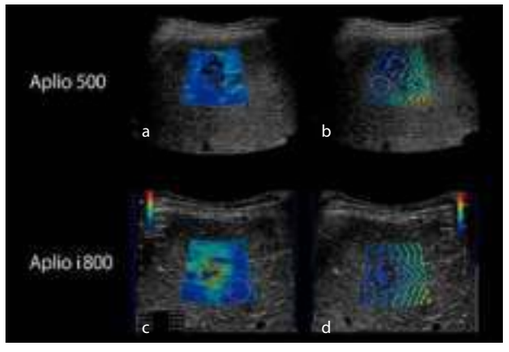


Figure 8 Comparison of Aplio 500 and Aplio i800 in a case of a 50 year-old female with liver metastasis

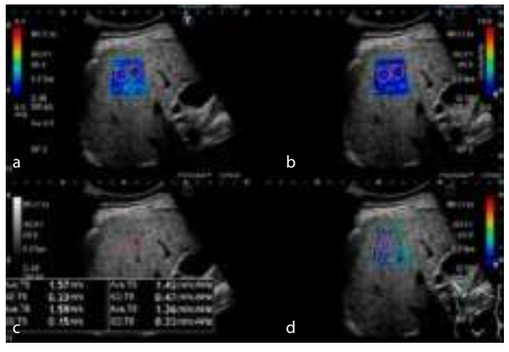


Figure 9 Shear Wave Elastography in QuadView: 70F, F3 NASH (a) SWE (b) SWD (c) Grayscale (d) Propagation map

Clinical value of SWE for assessing liver stiffness

Clinical cases of patients with different fibrosis staging were obtained at our institution in the period from January, 2014 to April, 2016. The liver stiffness was measured using two different ultrasound models and liver biopsy was performed. The correlation between the two ultrasound models were then compared. SWE results collected from Aplio i-series and Aplio 500 was compared with METAVIR Score (Fibrosis/Activity) from liver biopsy. In addition, the cutoff value for liver cirrhosis was obtained from the clinical evaluation.

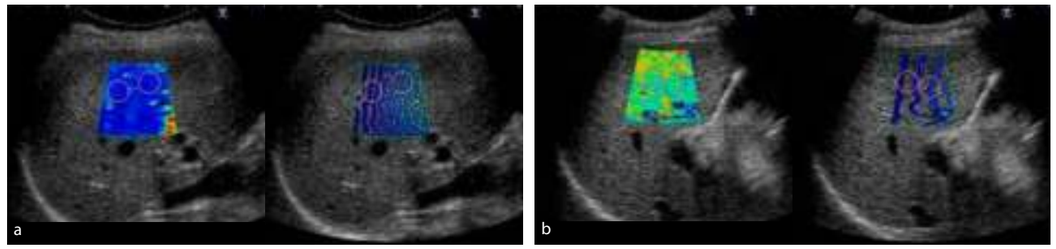
Following is a case of F1/A1 (chronic hepatitis) and a case of F4 (cirrhosis), with shear wave velocity of 1.51 m/s and 3.32 m/s respectively (Figure 10).

Based on the color scale, color changes from blue to yellow/red when the shear wave velocity increases. The contour lines in the Propagation Map are widely separated in F4. Both cases exhibit uniform propagation of shear waves. Large structures such as blood vessels are not mapped.

Transient elastography (TE, FibroScan®) is currently considered as a gold standard for fibrosis staging. It is reported that stiffness measured by TE is proportional to the risk of developing liver cancer, proving the importance of assessment on liver stiffness. An excellent correlation coefficient of 0.90 was obtained when comparing SWE with TE, demonstrating SWE as a reliable tool for analyzing fibrosis.

When evaluating liver stiffness with SWE, the shear wave velocity (m/s) increases as fibrosis progresses from F0 to F4 and there is a statistically significant difference between different fibrosis stages. In recent years, there has been an increasing trend in patients with liver inflammation, such as NASH and hepatitis. Fibrosis progression in chronic hepatitis is commonly accompanied by inflammation. However, there is only a statistically significant difference between A1 and A2.

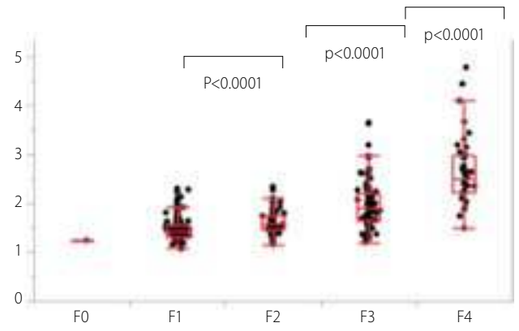
Based on the results obtained at our institution, the cutoff value for cirrhosis in SWE is 2.02 m/s. Patients who exhibit a shear wave velocity equal or higher than 2.02 m/s suggests a diagnosis of liver cirrhosis. The area under the ROC curve was 0.932, demonstrating the excellent diagnostic accuracy of SWE on examining cirrhosis.



Mean: 1.51 m/sec. F1, A1 (chronic hepatitis)

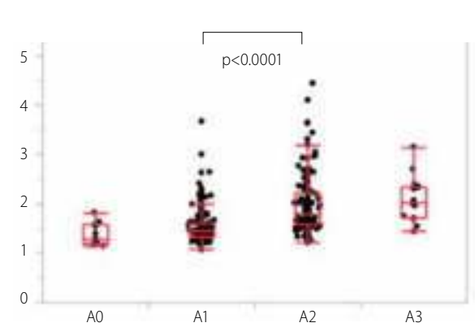
Mean: 3.32 m/sec. F4 (cirrhosis)

Figure 10 (a) A case of chronic hepatitis and a case of (b) cirrhosis



Fibrosis	F0	F1	F2	F3	F4
n	1	179	84	107	40
Vs (m/s)	1.24	1.46	1.62	1.96	2.66

(a) SWE (Vs) vs Fibrosis scores



Fibrosis	A0	A1	A2	A3
n	12	202	180	17
Vs (m/s)	1.38	1.55	1.95	2.10

(b) SWE vs Activity scores

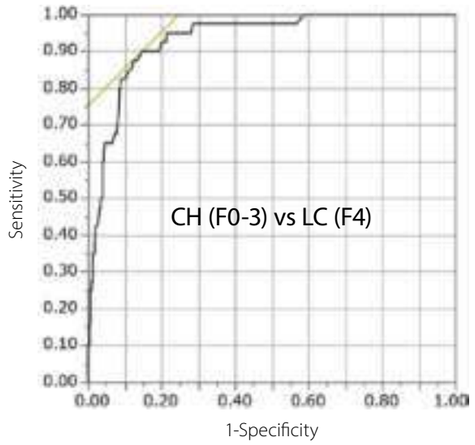
Figure 11 Comparison of SWE with liver biopsy using Metavir Score on fibrosis an activity.

Conclusion

Aplio SWE was found to be a reliable and effective tool for diagnosing fibrosis. SWE demonstrated excellent correlation with the state-of-the-art technologies, including liver biopsy and TE. Through clinical evaluation, it was confirmed that the shear wave velocity measured by SWE increases proportionally with the degree of fibrosis.

The propagation map makes it possible to observe whether the shear waves propagate smoothly through the liver tissue, allowing the reliability of the obtained data to be verified. With Aplio, it is expected that reliable data can be obtained in a single examination by observing the shear wave arrival time contours.

The elevated sensitivity in SWE data acquisition with Aplio i-series and Quad View functionality enable clinicians to perform SWE exams quicker and simpler.



AUCROC: 0.932

Vs	Sensitivity	Specificity
2.02	0.90	0.85

Figure 12 ROC curve for the diagnosis of liver cirrhosis using SWE. Area under the ROC curve is 0.932, demonstrating results with excellent diagnostic accuracy. Cutoff value for F1-F3 vs F4 is 2.02, assuming F4 to be positive.

Reference

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3. European Association for Study of Liver. "EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis." *Journal of hepatology* 63.1 (2015): 237.

Preliminary clinical experience with Shear Wave Dispersion Imaging for liver viscosity

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Introduction

Shear Wave Elastography (SWE) provides a quantitative measurement and real-time display of tissue elasticity. Literature reviews demonstrate that SWE is a fast and effective method for assessing liver fibrosis, though there is limitation when assessing patients with inflammation or steatosis. The main cause of the limitation is that viscosity properties are neglected in current algorithms for quantifying liver elasticity. In reality, liver tissue exhibits viscoelastic characteristics and the propagation of shear waves in the liver depends on both elasticity and viscosity. It is reported that liver diseases such as nonalcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD) or acute hepatitis, will increase the viscosity of the liver and this might affect stiffness assessment. Accurate stiffness quantification for liver diseases associated with steatosis and inflammation is therefore challenging. Early detection and treatment for acute hepatitis and the highly prevalent fatty liver allows the opportunity to reverse the deterioration. As a result, early detection is critical to take liver viscosity into account.

Shear Wave Dispersion Imaging (SWD), a new imaging technology, has been developed on the Aplio i-series for assessing the dispersion of shear wave, which is related to the viscosity properties in diffuse liver disease. In this paper, the feasibility of liver viscosity evaluation using SWD is studied through preliminary clinical evaluation.

Shear Wave Dispersion Imaging on Aplio i-series

Shear Wave Dispersion Imaging can be activated automatically in the Shear Wave Elastography mode. A Dispersion map provides visualization of the dispersion slope, which is a parameter directly related to viscosity. The calculated dispersion slope value (m/s/kHz) and its standard deviation are displayed. In SWE quad view mode (Figure 1), shear wave speed or shear wave elasticity (Speed Map, Elasticity Map), shear wave arrival time contour (Propagation Map), grayscale, and the dispersion slope (Dispersion Map) can be viewed simultaneously.

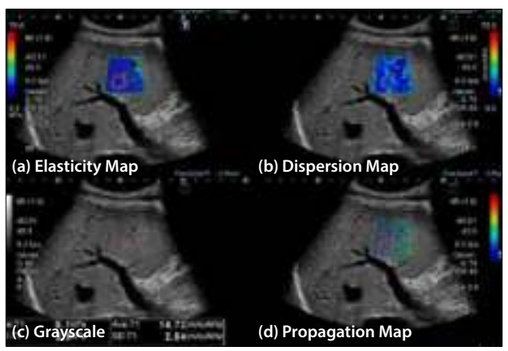

Figure 1 Quad View for SWE/SWD quantification.(a) Shear Wave Speed Map (b) Dispersion Map (c) Grayscale (d) Propagation Map

Principle of Shear Wave Dispersion Imaging

Liver is viscoelastic and shear wave speed depends on both elasticity and viscosity. In rheological models of viscoelastic material, viscosity (Pa·s) is represented as a damper and elasticity is represented as a spring (kPa). Viscosity is the measure of resistance to relative shearing motion, i.e. similar to a damper, tissue exhibits movement under gradual deformation instead of sudden deformation. Elasticity measures the ability of tissue to resist deformation and return to its original state, i.e. similar to a spring which contracts under pressure and expands when the pressure is released. There are two common viscoelastic models: Maxwell, represented by a spring and a damper connected in a series; and Voigt, represented by a spring and a damper connected in parallel.

Similar to Shear Wave Elastography, for assessment of viscosity, SWD measures the shear wave propagation generated through tissue deformation caused by a "push pulse". In current algorithms for SWE (kPa) quantification, the viscosity properties are neglected. In an example for elasticity calculation with the Voigt model, liver tissue is assumed to be perfectly elastic, thus shear elasticity is calculated by neglecting viscosity. By relating shear elasticity and Young's modulus E, elasticity E (kPa) can be acquired from shear wave propagation speed (Figure 3).

In reality, liver tissue has viscoelastic properties. Chronic diseases such as hepatitis or steatosis are considered to increase liver viscosity. In viscoelastic tissue, shear wave speed experiences frequency dispersion, which describes the change of shear wave speed, c_s depending on its shear wave frequency, *f*. The relationship between shear wave speed and shear wave frequency is observed using the Voigt model, i.e. shear wave speed is plotted against its frequency with different shear elasticity and shear viscosity (Figure 4). In perfectly elastic tissue, shear wave speed is constant regardless of the shear wave frequency. However, in viscoelastic tissue, shear wave speed does vary depending on the frequency. At a constant shear elasticity, with increased shear viscosity, there is an increase of slope, i.e. the slope demonstrates the degree of frequency dispersion (Figure 5). Dispersion and viscosity demonstrate a positive correlation.

Shear Wave Dispersion Imaging (SWD) is an innovative imaging technology for visualizing the dispersion (slope). It should be noted that SWD does not calculate viscosity directly, however, SWD has the advantage of obtaining actual quantification of dispersion, which is a parameter directly related to viscosity.

Shear Wave Dispersion Map

The Shear Wave Dispersion (SWD) Map provides visualization of the dispersion slope, allowing clinicians to estimate the viscosity of the liver.

Similar to SWE, a push pulse causes deformation of the liver tissue, generating shear waves. The displacement at each data point (A and B on Figure 6) is detected, time information and its displacement amplitude are acquired. By using a fast Fourier transform (FFT) algorithm, shear wave signals are converted to its shear wave frequency components. The shear wave frequencies obtained forms the x-axis for dispersion slope calculation. The shear wave speed is calculated for each frequency based on the displacement relationship among data points.

The shear wave speed calculated at each frequency is plotted on the y-axis. The slope of the shear wave speed is obtained as the dispersion value with a unit of m/s/kHz, representing shear wave speed versus shear wave frequency. Dispersion values are superimposed over the B-mode image and create the Dispersion map. By placing a measurement ROI on the Dispersion map, quantification of the dispersion slope can be obtained, and viscosity of the liver can be estimated.

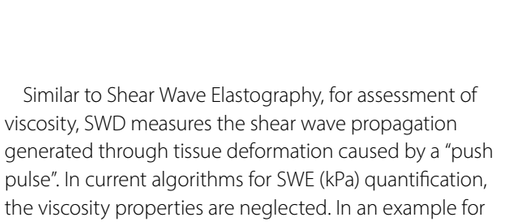

Figure 2 In rheological models of viscoelastic material, viscosity (Pa·s) is represented as a damper and elasticity is represented as a spring (kPa).

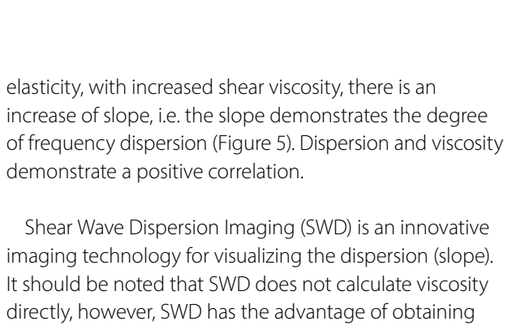

Figure 3 Current algorithm for obtaining elasticity (kPa)

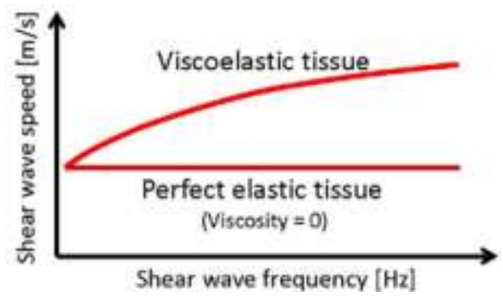

Figure 4 Relationship between shear wave speed and shear wave frequency in perfectly elastic tissue and viscoelastic tissue

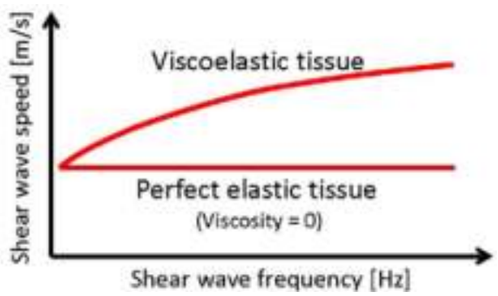

Figure 5 Viscosity and Dispersion (slope) have a positive correlation

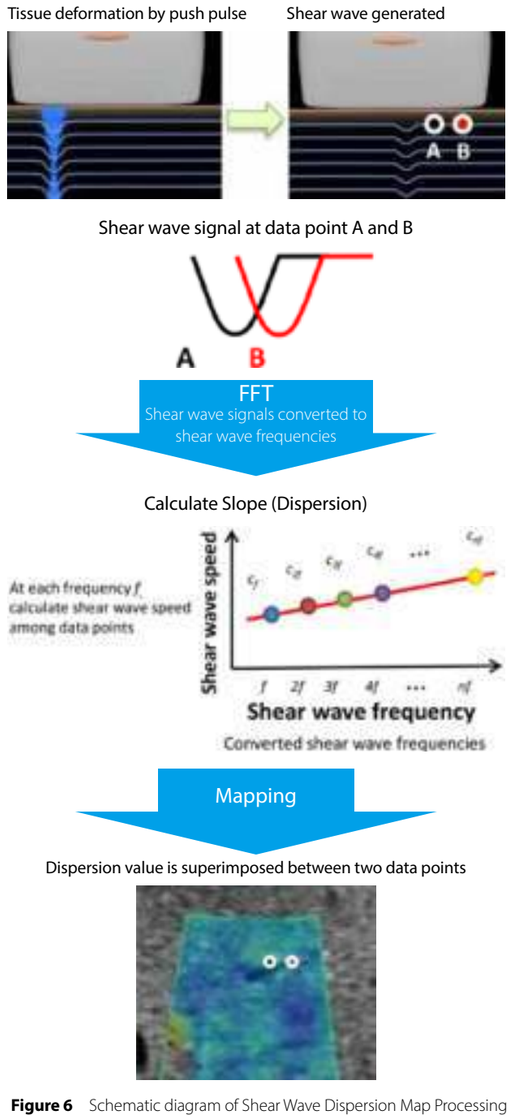

Figure 6 Schematic diagram of Shear Wave Dispersion Map Processing

Clinical evaluation

In our preliminary clinical experience with Shear Wave Dispersion Imaging, we quantified the viscoelasticity using SWE and the dispersion slope with SWD on patients with normal liver (control group), non-alcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), chronic hepatitis (HBV, HCV, alcoholic), liver cirrhosis (HCV, alcoholic), and acute hepatitis. The following cases are based on our preliminary study.

Case 1 (Figure 7) is a normal liver and case 2 (Figure 8) is a liver with NASH. NASH is a type of steatosis that demonstrates histologic evidence of hepatocyte injury, including hepatocellular ballooning, lobular inflammation, and/or liver fibrosis. Compared to a normal liver, NASH shows a slight increase in elasticity but remains in the normal range. However, there is an obvious increase in the dispersion slope.

In a case of acute hepatitis A infection (Case 3, Figure 9), the highly elevated AST and ALT values in the blood test are accompanied with a slight increase in elasticity but significant increase in dispersion slope.

In a case of NASH-LC (Case 4, Figure 10), the B-mode image did not reveal the characteristics of a fatty liver. Instead, NASH-LC has a slightly higher elasticity but an extremely high dispersion slope. In a case of HCV-induced cirrhosis (Case 5, Figure 11), elasticity is exceptionally high but with an obvious increase in dispersion slope.

Compared with NASH-LC, HCV-induced cirrhosis has an exceptionally high elasticity but the dispersion slope is not as high. In contrast, the dispersion slope of NASH-LC is extremely high but accompanied with a moderate increase in elasticity. Further study is necessary to confirm the relationship between elasticity and dispersion slope results versus histopathology.

The effect of the etiology on the dispersion slope and shear wave speed is obtained from the clinical evaluation. By sorting the results by etiology, a strong correlation can be observed (Figure 12). The results from NASH are grouped along a (yellow) slope which is tilting towards the dispersion slope axis, demonstrating that NASH has a stronger correlation with dispersion rather than shear wave speed. In comparison, data related to liver cirrhosis is mostly concentrated along the (green) slope which is tilting towards the shear wave speed axis, indicating that liver cirrhosis has a stronger effect on shear wave speed. Further clinical evaluation with a larger sample size is however recommended.

Conclusion

The preliminary clinical experience with Shear Wave Dispersion Imaging (SWD) indicates that elasticity is a more effective parameter for assessing hepatic fibrosis while viscosity is more effective in assessing necroinflammatory change and fat deposition. In addition to conventional viscoelasticity imaging with shear wave, SWD is an innovative imaging technique that offers viscosity evaluation with a potential for additional pathophysiological insights on clinical evaluation of the liver.

Reference

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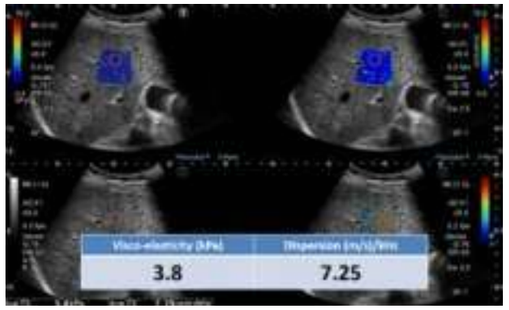

Figure 7 Case 1: Normal Liver
PLT: 309 × 103 μL, AST: 19 U/L, ALT: 13 U/L, T-Bil: 0.4 mg/dL

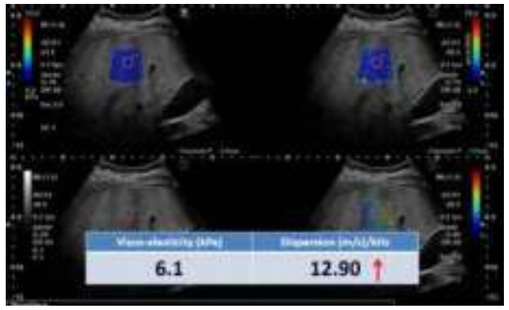

Figure 8 Case 2: NASH
PLT: 248 × 104 μL, AST: 78 U/L, ALT: 172 U/L, T-Bil: 0.42 mg/dL

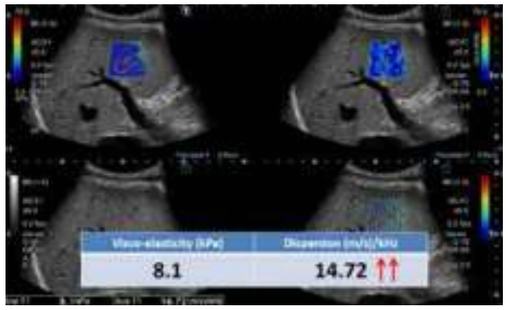

Figure 9 Case 3: Acute Hepatitis A infection
PLT: 134 × 103 μL, AST: 6760 U/L, ALT: 7698 U/L, T-Bil: 4.59 mg/dL

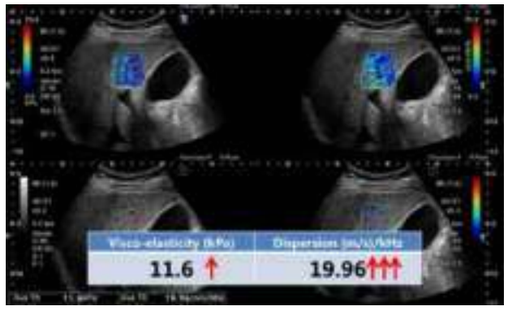

Figure 10 Case 4: NASH-LC
PLT: 4.6 × 103 μL, AST: 48 U/L, ALT: 49 U/L, T-Bil: 1.10 mg/dL

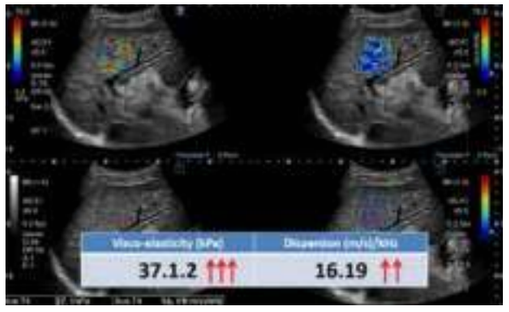

Figure 11 Case 5: HCV-induced cirrhosis
PLT: 113 × 103 μL, AST: 85 U/L, ALT: 62 U/L, T-Bil: 0.94 mg/dL

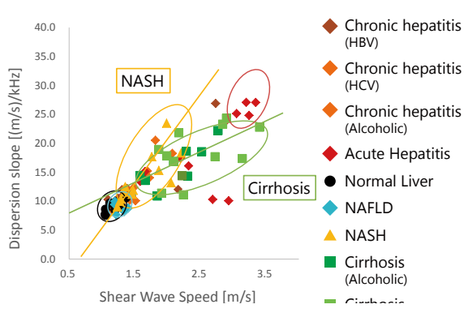

Figure 12 Correlation between Shear Wave speed and Dispersion slope in clinical evaluation

Assessment of non-alcoholic fatty liver disease with Attenuation Imaging (ATI)

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Introduction

The four major liver diseases worldwide are HBV, HCV, alcoholic liver disease and nonalcoholic fatty liver disease (NAFLD). Recently, there is an increasing trend for fatty liver that is highly associated with risk factors including obesity, diabetes, hyperlipidemia, and hypertension. Among the Japanese population 15M to 20M people have these risk factors, which represents about one in eight amongst the population being associated with fatty liver, including non-alcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH). It is estimated that in Japan around 3M to 4M people have NASH and the incidence is expected to increase .

It is reported by the Japanese Diabetes Society that diabetic patients are 2-3 times more likely to develop liver cancer. In our institute, we have concluded that patients with diabetes associated with liver fibrosis have a higher risk of developing liver cancer, especially HCV-induced liver cancer. Thus, we strongly recommended strict follow up on diabetic patients with liver fibrosis.

Our institute collected 1343 HCC cases between 2007 and 2016. Until 2010, about 20% of the cases were non-HBV/HCV-induced HCC which had increased to 32% by 2017, similar to global trends. This significant increase of non-HBV/HCV induced HCC is related to primary liver cancer developed from fatty liver. As a result, early detection and characterization of liver steatosis is important in order to provide better patient management. Attenuation Imaging (ATI) is an innovative application embedded on the Aplio i-series to access liver attenuation by quantifying the attenuation coefficient and to provide color mapping for the degree of attenuation. In this white paper, the assessment of non-alcoholic fatty liver disease with ATI is studied.

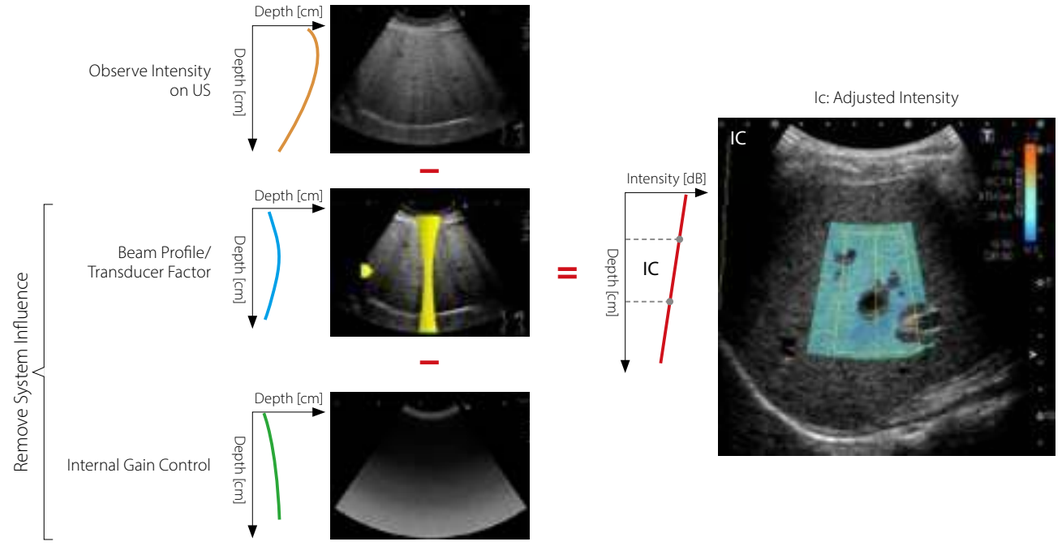


Figure 1 Principle of ATI

Principle of ATI

Attenuation of ultrasound signals depends on the tissue structure and acoustic characteristics of the liver parenchyma. Fatty liver is associated with increased ultrasound signal attenuation. Due to decreased signal intensity, especially in deeper regions, fatty liver often contributes to ultrasound images with poor image quality.

In order to calculate the attenuation coefficient (dB/cm/MHz) with ATI, the system influence on signal intensity is removed by extracting the focus dependent beam profile (dB) and internal gain control (dB) from the observed intensity on the ultrasound image. The adjusted intensity demonstrates the change of intensity with depth in the region of interest (ROI).

In ATI, the extracted pure intensity change is represented by a line profile. Each sample point on the line profile is obtained by averaging intensity along the same depth. In patients with higher attenuation, there will be more of a decrease in intensity, resulting in a steeper line profile. The slope of the extracted intensity is related to the attenuation coefficient.

Features of ATI can be reviewed in an image with an ATI measurement (Figure 2). The level of attenuation is color-coded and displayed in the ROI. Regions with significant errors of attenuation calculation such as structures (blood vessels) or areas with strong artifacts (reverberation) are excluded on the ATI map. Since only the reliable areas for measurement are displayed, accurate ATI measurement can be acquired quickly and easily. In addition, the coefficient of determination (goodness of fit) is displayed along with the attenuation coefficient, allowing clinicians to confirm the optimal location for ROI placement in order to improve accuracy.

$$\alpha = -\frac{1}{2f}\frac{dI_c}{dz}$$

α : Attenuation coefficient [dB/cm/MHz]
Ic : Adjusted Intensity [dB]
f : Central Frequency [MHz]
z : Depth [cm]

Equation 1 Definition of attenuation coefficient

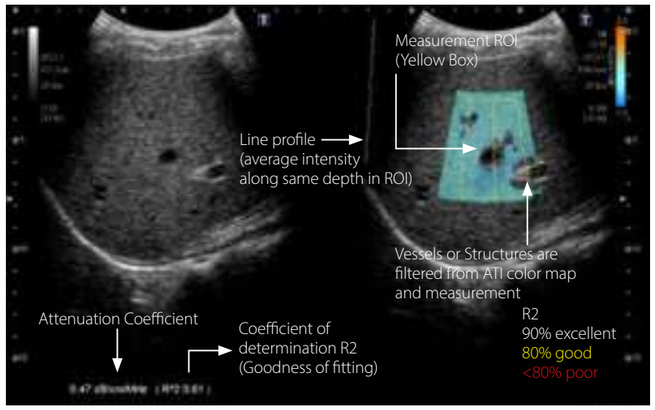
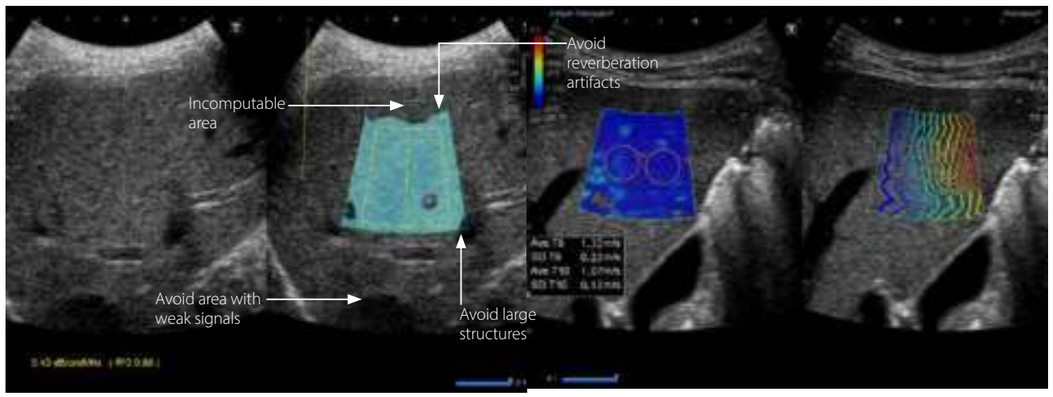


Figure 2 ATI measurement features



CAP : 165 dB/m (0.47 dB/cm/MHz), ATI : 0.43 dB/cm/MHz

Figure 3 Normal Liver. During ATI measurement, it is important to avoid unreliable areas. ATI and CAP measurement for normal liver demonstrated consistent attenuation scoring.

Correlation between ATI and state-of-the-art for liver steatosis

Clinical evaluations were performed to compare ATI with Controlled Attenuation Parameter (CAP, FibroScan®). Figure 3 shows a case of a normal liver. CAP and ATI demonstrated consistent attenuation scoring. In order to obtain reliable ATI measurements, it is important to avoid areas with reverberation artifacts, structures or weakened signals.

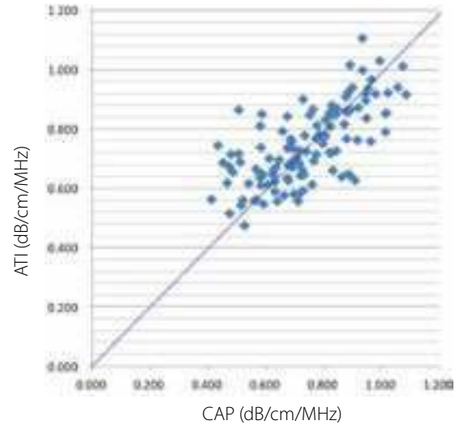


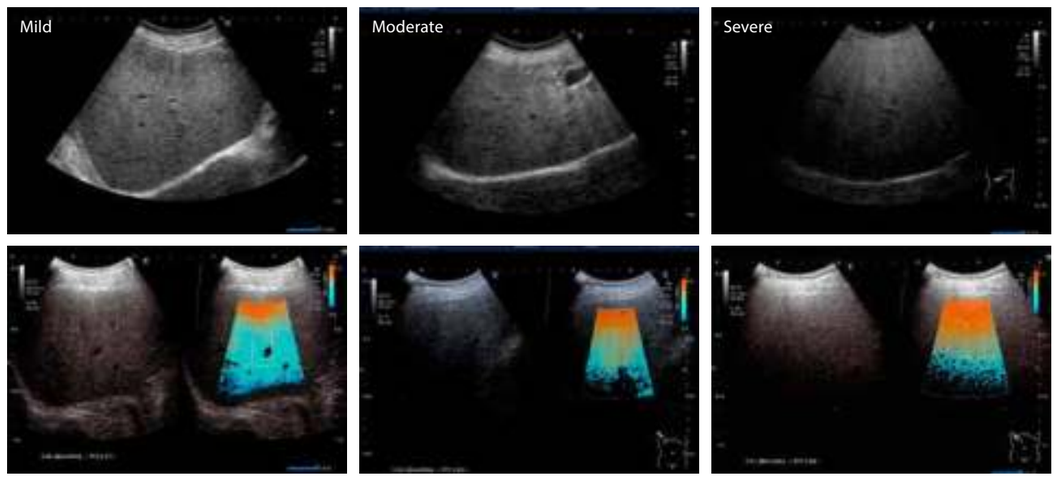
Figure 4 Correlation between ATI and CAP

In 118 cases of liver steatosis, ATI and CAP demonstrated a good correlation (r = 0.69) (Figure 4).

Figure 5 demonstrates the comparison between ATI versus CAP and CT measurements in mild, moderate, and severe fatty liver. According to literature reviews, a patient is diagnosed with fatty liver when the CT liver-to-spleen (L/S) attenuation ratio is less than 1.0 or 1.1; and liver fat content is greater than 30%. ATI and CAP exhibit an excellent correlation with the CT L/S ratio.

We examined the relationship between ATI and patient background factors including age, BMI, and blood test results. Based on univariate and multivariate analysis, ATI has a statistically significant difference with B-mode steatosis grading, distance of skin to the liver capsule and BMI, which are conventional factors for assessing steatosis.

In our institute, the protocol for assessing fatty liver with B-mode, includes scanning with consistent intensity (dB) and dynamic range (DR) at the intercostal space. Automatic gain correction, gamma correction and compounding are switched off to avoid system influence on intensity. Liver-to-kidney ratio is used for assessing liver steatosis and the grading is as follows: mild fatty liver with increased echogenicity and complete delineation of vasculature and diaphragm; moderate fatty liver with partial viewing (<75%) of vasculature and diaphragm; and severe fatty liver with poor viewing (< 50%) of vasculature and diaphragm. This diagnostic criteria of liver-to-kidney



Modality	Mild
CAP	0.634* (222 dB/m)
ATI	0.672*
CT (L/S)	1.35
Histology	NA

Modality	Mild
CAP	0.871* (305 dB/m)
ATI	0.818*
CT (L/S)	1.03
Histology	20%

Modality	Mild
CAP	0.97* (341 dB/m)
ATI	0.938*
CT (L/S)	0.73
Histology	NA

* In dB/cm/MHz. Average value after 10 measurements.

Figure 5 Diagnosis of steatosis with ATI, CAP and CT L/S ratio in mild, moderate and severe fatty liver

ratio has an excellent correlation with ATI.

When investigating the correlation between CAP and ATI with histopathology, CAP has a higher variation when quantifying severe fatty liver. In contrast, ATI exhibits less variation and is able to diagnose very mild fatty liver (steatosis < 10%, histology). For histological steatosis, the degree of fatty liver is staged as normal (<10%), mild (10-33%), moderate (33-66%) and severe (>66%) respectively. Based on the NASH/NAFLD Diagnosis Guide (2015) from the Japanese Society of Gastroenterology, it is important to diagnose very mild steatosis at 5-10% for early patient management. With the early detection of very mild steatosis, a patient is able to easily reverse a fatty liver through exercise and diet therapy.

The correlation between CT L/S ratio with ATI was also evaluated. On CT, three ROIs with a diameter of 2 cm were placed on the liver and spleen respectively to obtain the average L/S ratio. Fatty liver is diagnosed when L/S is <1.0. Both ATI and CAP demonstrated a good correlation with the CT L/S ratio, and especially ATI shows less variation and exhibits a more stable result. When evaluating 57 cases with an L/S ratio >1.0, 10 (18%) cases were subsequently diagnosed as fatty liver with B-mode grading, implying that CT may overlook fatty liver.

In addition, the relationship between histopathology findings versus CAP, ATI and CT L/S ratio were evaluated. When compared to histopathology, CT has some limitations in diagnosing mild fatty liver but is reliable when diagnosing severe fatty liver. In contrast, ATI is able to diagnose very mild steatosis (<10%) and mild steatosis (10-30%). As a result, with ATI, ultrasound demonstrates a higher potential for diagnosing mild steatosis.

Diagnosis of NASH using ATI

In recent years, the criteria for NASH classification has gradually been updated, the Brunt system utilizing a combination of grading and staging is now one of the standard methods to classify NASH. According to the "NASH / NAFLD clinical guide 2015", it is necessary to stage steatosis levels as 5%, 20%, 40%, 60% or 80% respectively, a scale within which very mild steatosis is indicated.

Although there is no correlation between steatosis grading in simple steatosis and life expectancy, simple steatosis in the process to fibrosis is reported to have an overwhelmingly negative prognosis. In other words, NAFLD patients with fibrosis require strict follow up.

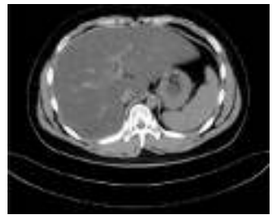
The following are 2 clinical cases with NASH.

A man in his early 20's is diagnosed with NASH in ulcerative colitis (Figure 6). CT L/S ratio confirmed the steatosis. From B-mode, the speckle pattern of liver parenchyma does not provide an indication of fibrosis, however the beginning of fibrosis could be confirmed based on the obvious increase in ALT (101 IU /L) and PLT (290,000 / μL) from a blood test, and from histology findings. Both SWE (1.56m/s) and FibroScan (1.98m/s) exhibit a high value in liver stiffness. If early therapy is not conducted, it is predicted that NASH will proceed to liver cirrhosis before he reaches his 40s. Early detection is essential in this type of case for the patient's ongoing quality of life.

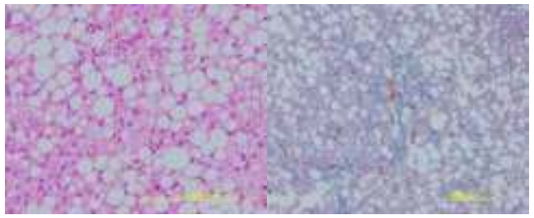
When liver cirrhosis progresses, the extent of steatosis will decrease. Case 2 is of burnt-out NASH in a 60-year-old female (Figure 7). NASH has progressed to liver cirrhosis with an obvious increase of fibrosis. With liver biopsy, the patient is diagnosed with F4 and steatosis of 8%. In order to fully investigate burnt-out NASH, both fibrosis and steatosis are need to be properly examined.

Feasibility of comprehensive diagnosis using ATI and SWE

When assessing liver disease, liver stiffness can be measured using SWE and steatosis can be quantified by analyzing the attenuation with ATI. By comprehensive evaluation with SWE and ATI, fibrosis staging and steatosis scoring can be performed and may be able to characterize normal liver, fatty liver, burn-out-NASH, and NAFLD. The characterization by the multi-parameter method is important as it is critical to detect very mild steatosis with fibrosis for early detection of incidence of liver cirrhosis.

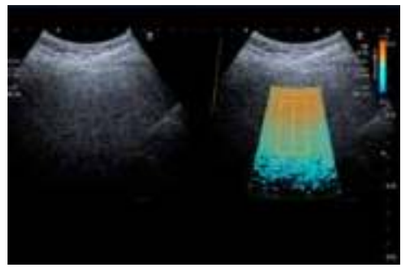


CT (Liver : 7.6 L/S : 0.17)

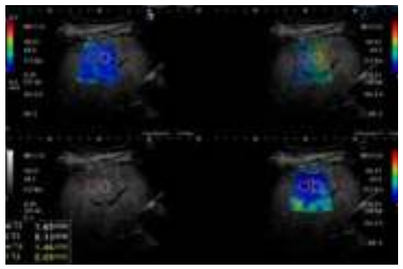


Liver Biopsy : F4, A2, Steatosis 90%

Blood Test	NASH
ALT	101
PLT x 10^3	29.4
HLA	32
M2BPGi	0.38



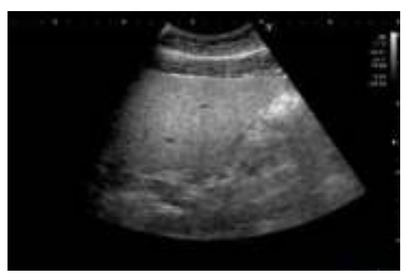
US (ATI : 0.942)

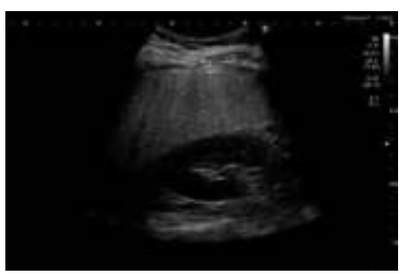


US (SWE : 1.56)

	i800	CAP
ATI/CAP (dB/cm/MHz)	0.942	0.9 (315 dB/m)
SWE (m/s)	1.56	1.98 (11.8 kPa)

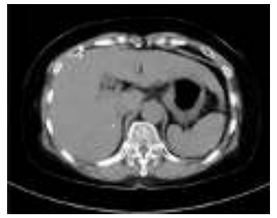
Average value after 10 measurements.



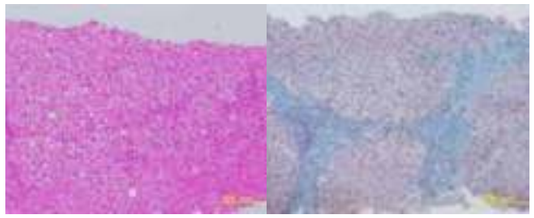


US (Fatty Liver : Severe)

Figure 6 Case 1: NASH with ulcerative colitis

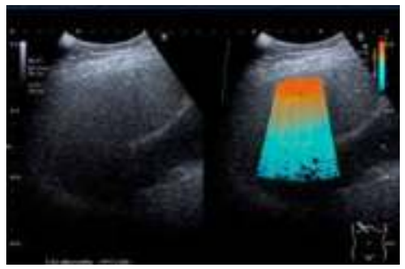


CT (Liver : 50.1 L/S : 1.09)

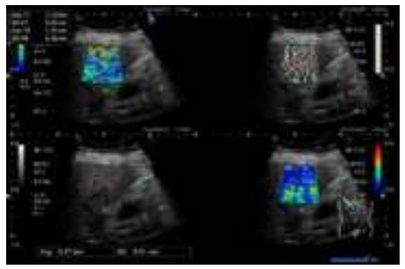


Liver Biopsy : F2, A2, Steatosis 8%

Blood Test	NASH
ALT	19
PLT x 10^3	11.5
HLA	393
M2BPGi	2.42



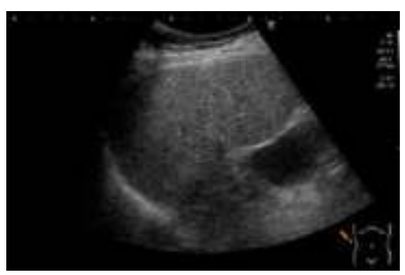
US (ATI : 0.874)

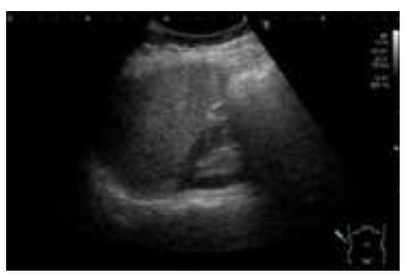


US (SWE : 2.41)

	i800	CAP
ATI/CAP (dB/cm/MHz)	0.874	0.92 (322 dB/m)
SWE (m/s)	2.41	3.20 (30.8 kPa)

Average value after 10 measurements.





US (Fatty Liver : Moderate)

Figure 7 Case 2: 60F with Burn out NASH.

Conclusion

Attenuation Imaging (ATI) demonstrates an excellent correlation with CAP and has a statistically significant difference with B-mode grading. Both CAP and ATI have a strong negative correlation with CT, which can clearly detect severe fatty liver but the diagnosis of mild fatty liver remains more challenging.. On the other hand, ATI is able to differentiate mild steatosis (< 30%). Ultrasound can realistically provide a quick, non-invasive, cost-effective and radiation-free method to diagnose mild liver steatosis. Furthermore, in addition to fatty liver diagnosis, there is a high potential for morphologic or histologic steatosis assessment with comprehensive diagnosis using ATI and SWE on the Aplio i-series.

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