Canon

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

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Introduction

The four major liver diseases worldwide are Hepatitis B and Hepatitis C virus (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 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 recommend 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 assessment and characterization of liver steatosis is important in order to provide better patient management. Attenuation Imaging (ATI) is an innovative application embedded in 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.

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) (Figure 1 and Equation 1).

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

α : Attenuation coefficient [dB/cm/MHz]
Ic : Adjusted Intensity [dB]
f : Central Frequency [MHz]
z : Depth [cm]
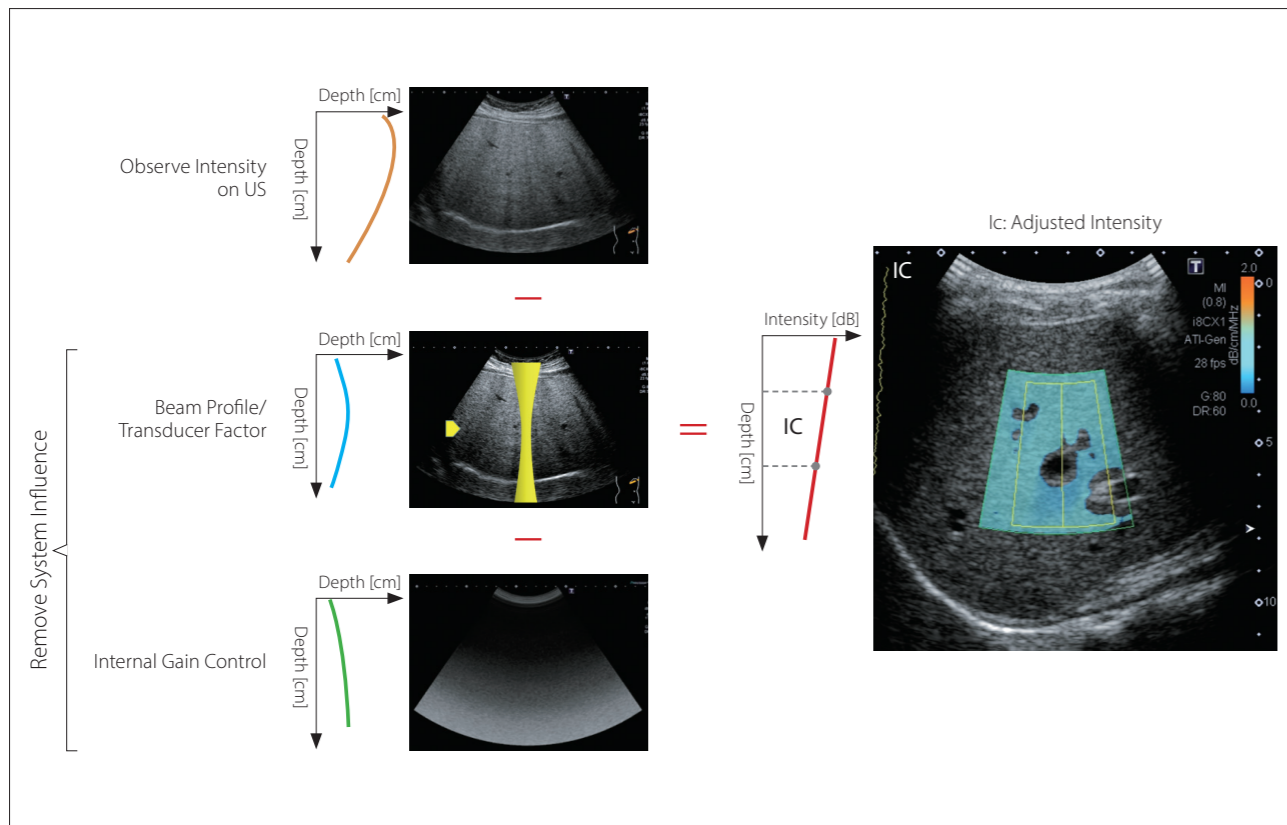
Equation 1 Definition of attenuation coefficient

Made For life

Figure 1 Principle of ATI
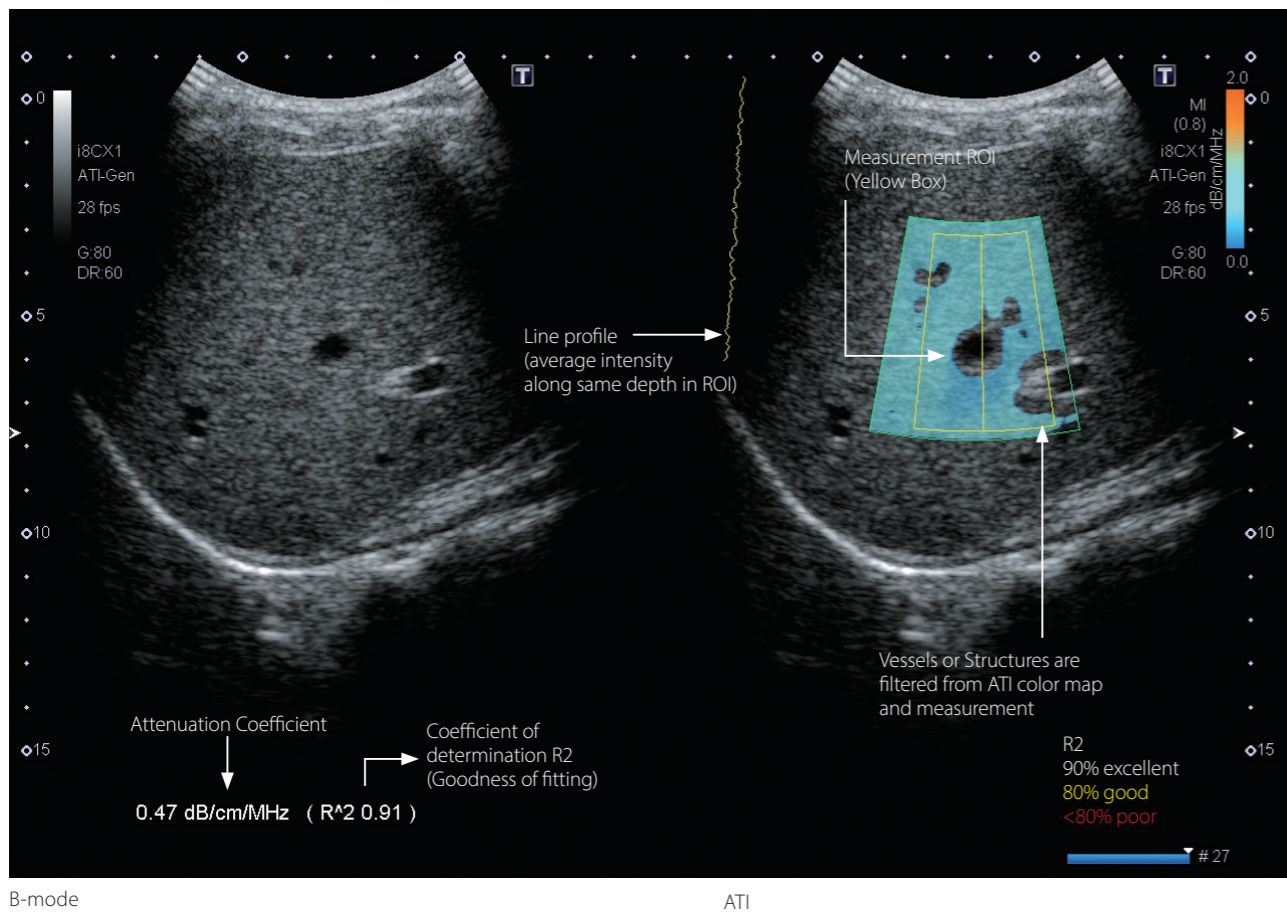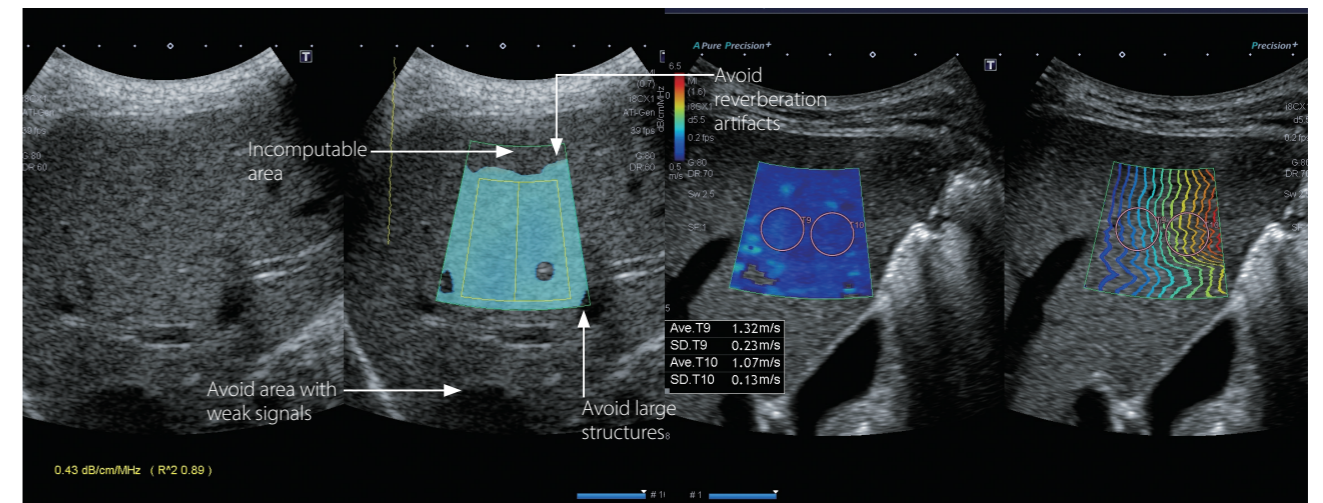

B-mode

ATI

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.

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.

Figure 4 Correlation between ATI and CAP

Correlation between ATI and current methods for assessing liver steatosis

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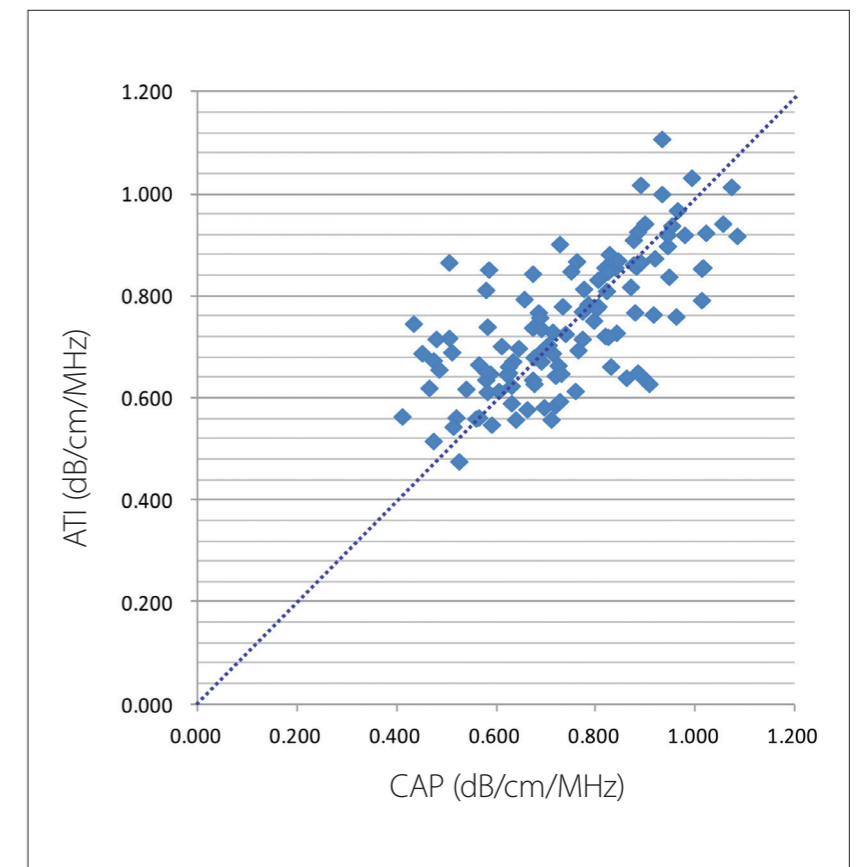ase of a normal liver. CAP and ATI demonstrated consistent attenuation scoring. In order to obtain reliable ATI measurements, it is important to avoid areas with reverberation artifacts, structures or weakened signals.

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 criterion of liver-to-kidney 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 provide assessment of 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 the assessment of mild fatty liver but is reliable in 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.
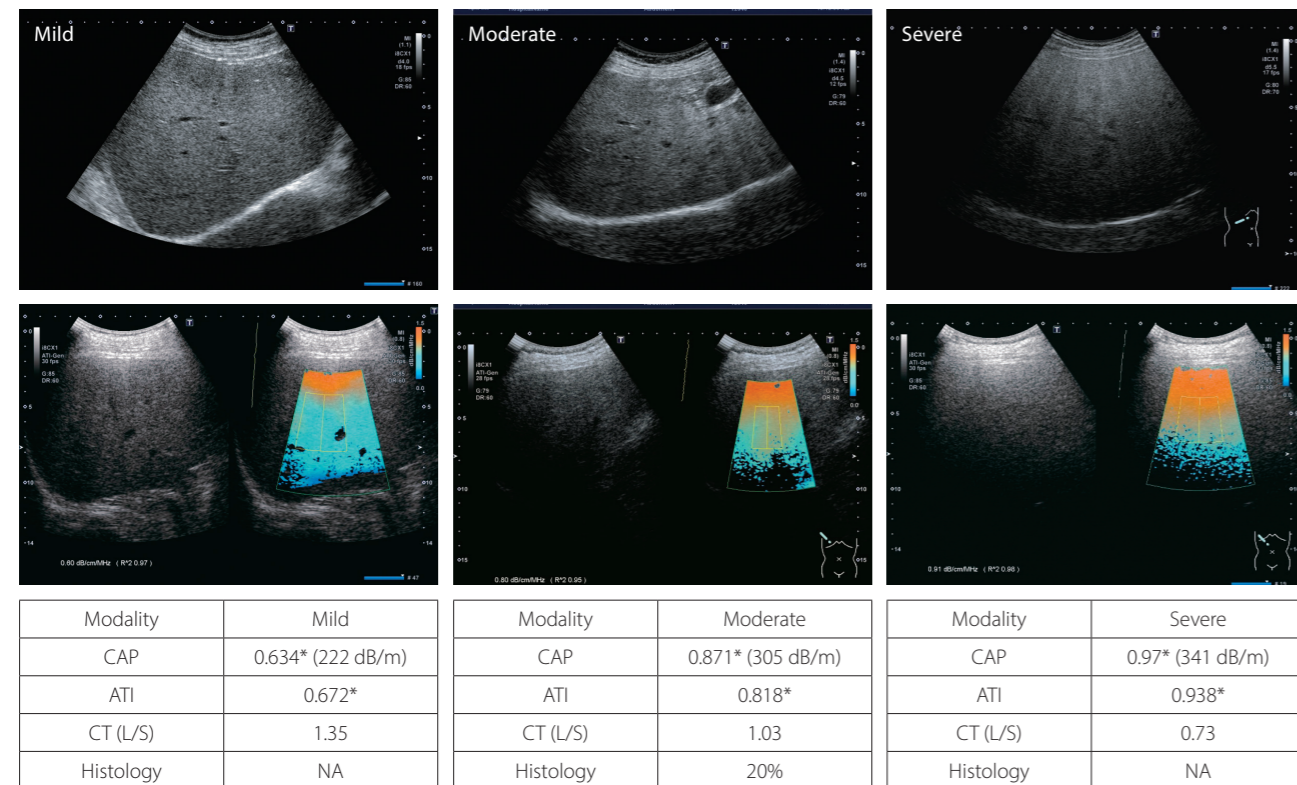
Diagnosis of NASH using ATI

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 progression 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 management is essential in this type of case for the patient's ongoing quality of life.

CT (Liver : 7.6 L/S : 0.17)   Liver Biopsy : F2, 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

Mild	Moderate	Severé

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

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

Modality	Severe
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.

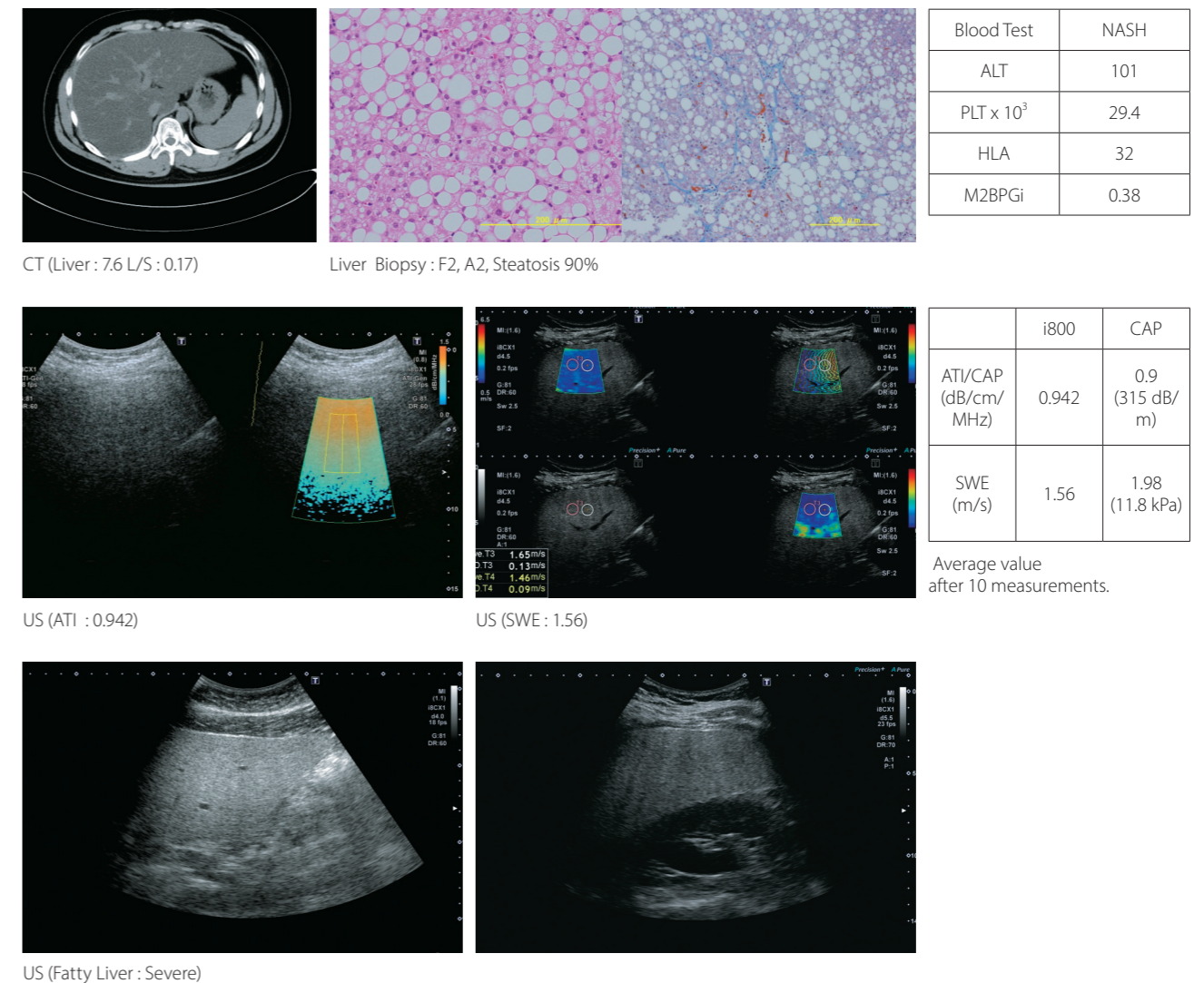**Figure 5**   Diagnosis of steatosis with ATI, CAP and CT L/S ratio in mild, moderate and severe fatty liver

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 need to be properly examined.
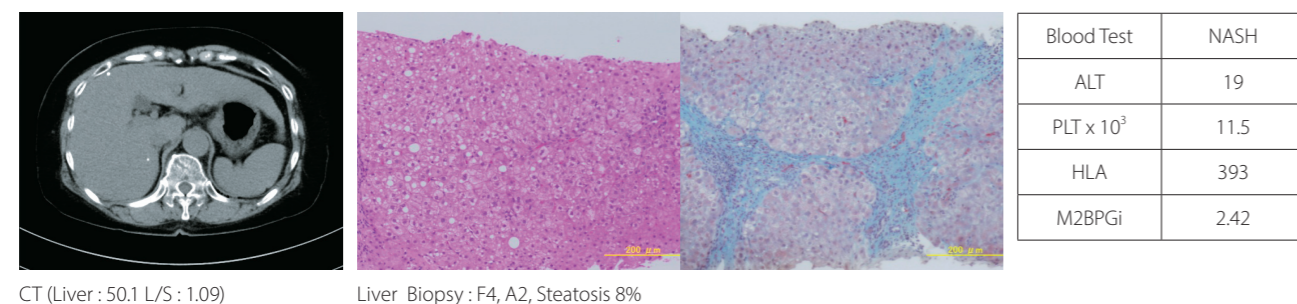
Feasibility of comprehensive diagnosis using ATI and SWE

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. This characterization by the multi-parameter method is important as the assessment of mild steatosis

with fibrosis is critical, which may allow interventions to help reduce the likelihood of cirrhosis.
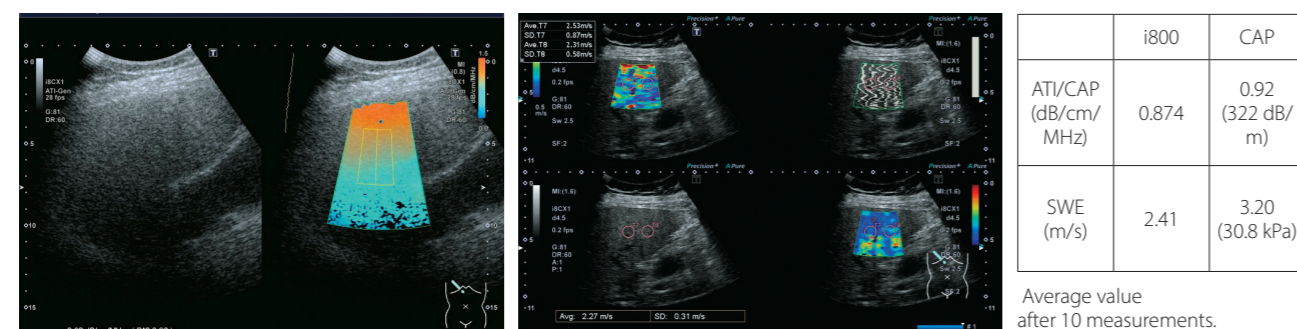
Conclusion

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 visualize 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.
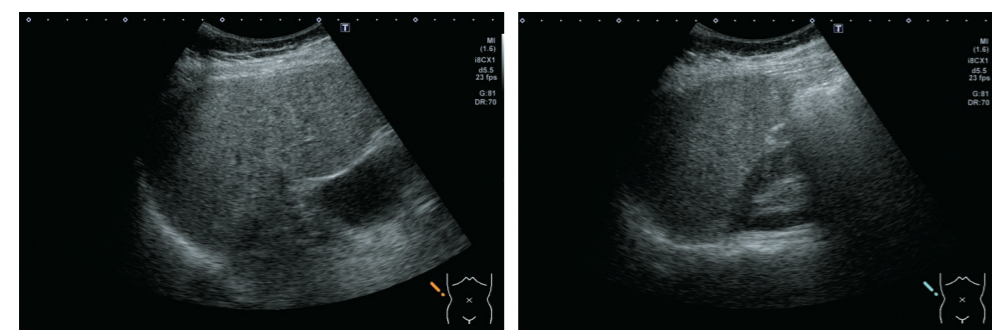

CT (Liver : 50.1 L/S : 1.09)

Liver Biopsy : F4, 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.

References

1. Angulo, Paul, et al. "Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease." Gastroenterology 149.2 (2015): 389-397.
2. Aoki, Tomoko, et al. "Prediction of development of hepatocellular carcinoma using a new scoring system involving virtual touch quantification in patients with chronic liver diseases." Journal of gastroenterology 52.1 (2017): 104-112.
3. Bedossa, Pierre, Delphine Dargère, and Valerie Paradis. "Sampling variability of liver fibrosis in chronic hepatitis C." Hepatology 38.6 (2003): 1449-1457.
4. Iwasaki, Minoru, et al. "Noninvasive evaluation of graft steatosis in living donor liver transplantation." Transplantation 78.10 (2004): 1501-1505.
5. Masuzaki, Ryota, et al. "Prospective risk assessment for hepatocellular carcinoma development in patients with chronic hepatitis C by transient elastography." Hepatology 49.6 (2009): 1954-1961.
6. Park, Yang Shin, et al. "Biopsy-proven nonsteatotic liver in adults: estimation of reference range for difference in attenuation between the liver and the spleen at nonenhanced CT." Radiology 258.3 (2011): 760-766.
7. Sakamoto, Michiie, et al. "Pathological findings of nonalcoholic steatohepatitis and nonalcoholic fatty liver disease." Pathology international 67.1 (2017): 1-7.
8. Yezaz Ahmed Ghouri, Idrees Mian et al. "Review of hepatocellular carcinoma: Epidemiology, etiology, and carcinogenesis" J Carcinog. (2017):16: 1.
9. https://www.nhs.uk/conditions/liver-disease/
10. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4918764/
11. Author reference and Yoshito Tsushima, Keigo Endo Spleen Enlargement in Patients with Nonalcoholic Fatty Liver Dig Dis Sci (2000) 45: 196 and Liver Diseases—Advances in Research and Treatment: 2012 Edition ScholarlyEditions, 2012
12. Seung Soo Lee and Seong Ho Park Radiologic evaluation of nonalcoholic fatty liver disease World J Gastroenterol. 2014 Jun 21; 20(23): 7392–7402
13. J Gastroenterol. 2015 Apr;50(4):364-77. doi: 10.1007/ s00535-015-1050-7. Epub 2015 Feb 24. Evidence-based clinical practice guidelines for nonalcoholic fatty liver disease/nonalcoholic steatohepatitis. Watanabe S1, Hashimoto E, Ikejima K, Uto H, Ono M, Sumida Y, Seike M, Takei Y, Takehara T, Tokushige K, Nakajima A, Yoneda M, Saibara T, Shiota G, Sakaida I, Nakamuta M, Mizuta T, Tsubouchi H, Sugano K, Shimosegawa T; Japanese Society of Gastroenterology; Japan Society of Hepatology