Ultrasound / White paper

# Steatotic Liver Disease: What you should know

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## Introduction

Steatotic liver disease (SLD), formerly known as fatty liver, is emerging as the leading chronic liver disease worldwide. SLD has been proposed by several multinational liver societies as a new nomenclature to replace the widely used term, nonalcoholic fatty liver disease (NAFLD), to define the disease category by inclusion criteria rather than excluding several conditions, to focus on its pathophysiology related to metabolic dysfunction, and defuse the stigma caused by the terms fatty and alcoholic.

The global prevalence of obesity, defined as a body mass index (BMI) of 30 kg/m$^2$ or more, is increasing and has nearly tripled since 1975, largely due to sedentary lifestyles and unhealthy diets. More and more countries have shown high rates of obesity in recent decades; the regions with the highest rates are the United States and European countries. However, obesity is now increasing in other areas such as Africa and Asian countries[1].

Since the prevalence of SLD increases with the degree of obesity, SLD is expanding worldwide, reflecting the growing global obese population. According to a meta-analysis, its incidence in adults is estimated to be 24%.

Figure 1 shows the prevalence of SLD in different countries.

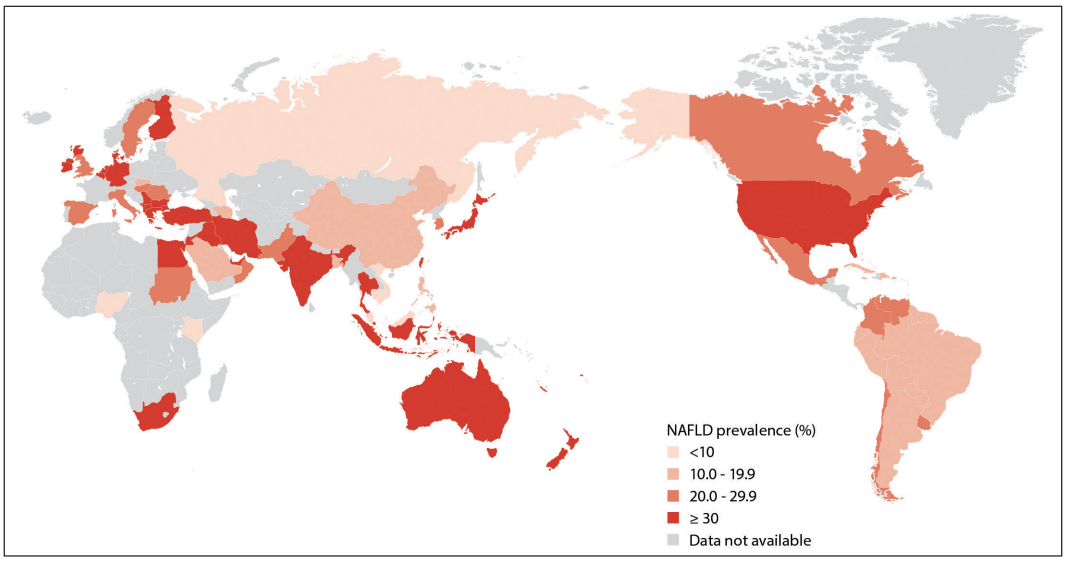



**Figure 1** NAFLD prevalence

Salmon-pink indicates a low-frequency area, as the incidence increases, the color changes to red. The prevalence of SLD in Japan is in the highest category (≥30%), even though the rate of obesity is much lower than in the United States. Genetic factors may partially explain this discrepancy; according to the global distribution of the single nucleotide polymorphism (SNP) of the PNPLA3 gene, the most significant SNP associated with SLD, approximately 40% of the Japanese population has the disease susceptibility allele (aleli)[2].

Overeating, especially excess simple sugars, and physical inactivity predispose to both metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic syndrome. Excess sugars are converted to triglycerides in the liver via de-novo lipogenesis. Fatty acid is also supplied from visceral fat by lipolysis. Also, hyperinsulinemia, which compensates for insulin resistance, promotes de novo lipogenesis in the liver.

Figure 2 is a representative case of hyperinsulinemia causing liver steatosis. An ultrasound image shows a hypoechoic area surrounded by an irregularly shaped hyperechoic lesion, indicating metastasis of insulinoma and localized liver steatosis caused by insulin secreted by the tumor.

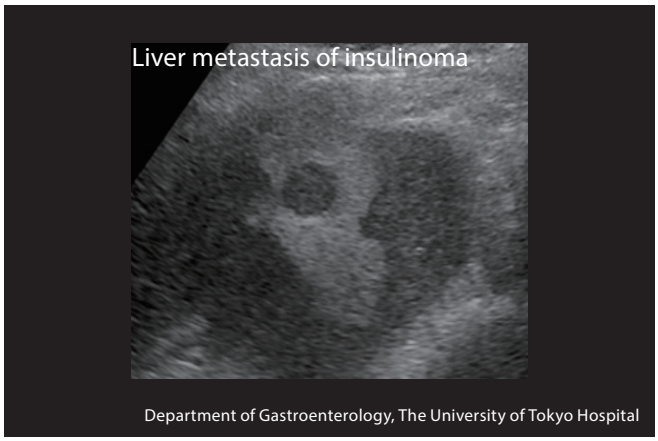



**Figure 2** MASLD is a manifestation of metabolic syndrome in the liver

## NAFLD to SLD

The disease concept of nonalcoholic steatohepatitis (NASH) was first proposed by Ludwig at Mayo Clinic in 1980. He reported a case series of patients whose biopsy specimens showed lobular inflammation and Mallory's hyaline in the fatty liver, features thought to be specific to alcoholic hepatitis at that time. However, these patients were non-drinkers and were characterized by obesity, diabetes, and cardiovascular disease[3].

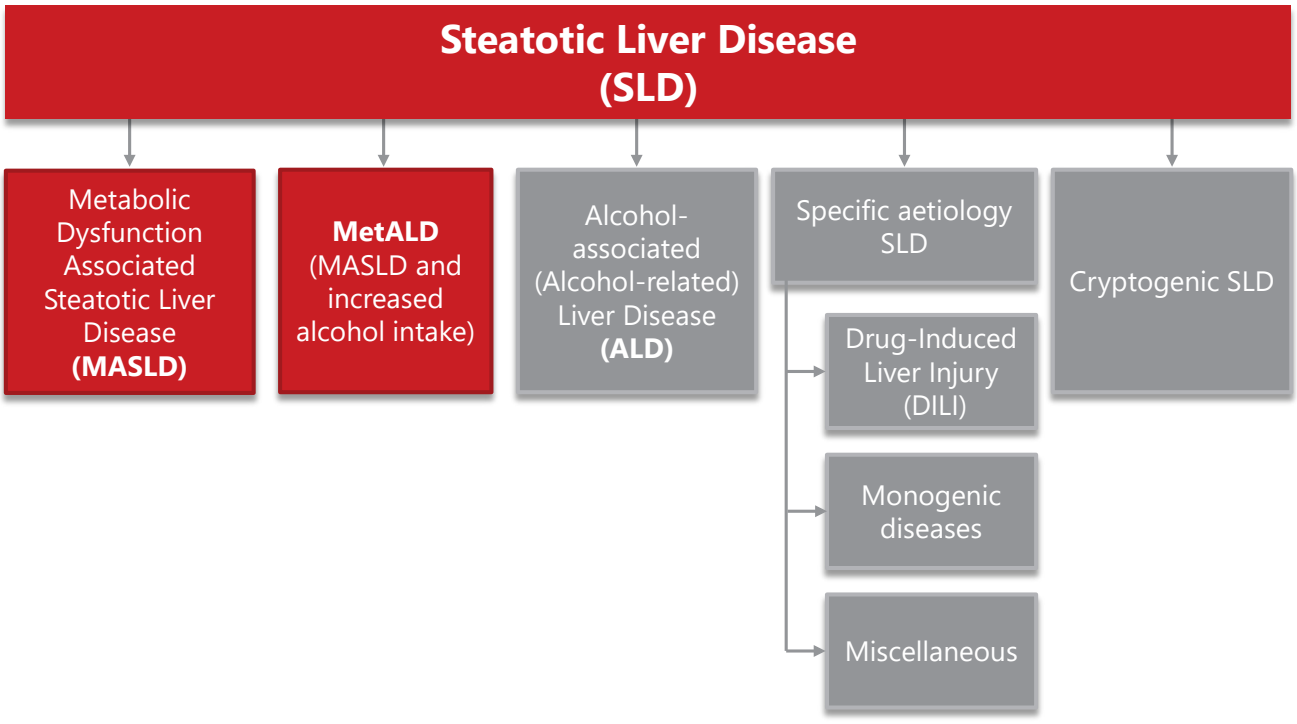
Twenty years later, Matteoni and colleagues proposed a classification of NAFLD based on follow-up data. He classified patients with NAFLD into 4 subgroups according to the presence of lobular inflammation, hepatocyte ballooning, Mallory's hyaline and fibrosis: type 1, fatty liver alone; type 2, fat accumulation and lobular inflammation; type 3 fat accumulation and ballooning degeneration; type 4, fat accumulation, ballooning degeneration, and either Mallory's hyaline or fibrosis. The prevalence of liver-related death was almost 0% for types 1 and 2, whereas it was 5% and 13% for types 3 and 4, respectively[4]. Later, Matteoni's type 3 and type 4 are called NASH, and the others are called nonalcoholic fatty liver (NAFL).

Since then, the terms NAFLD and NASH have been widely used. However, there has been an argument regarding the definition of NAFLD. The most important one is its exclusion criteria for moderate drinkers with a certain amount of alcohol intake over the strict criteria for NAFLD because some of those people show a similar phenotype with NAFLD and NASH. In addition, there is a motivation to emphasize its strong relationship with metabolic factors as the understanding of the background mechanism of the disease advances.

The American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) proposed a new nomenclature called Steatotic Liver Disease (SLD). Figure 3 shows the concept and the subclassification of SLD. Any fatty liver disease diagnosed by pathology or imaging is considered SLD. MASLD is defined as the presence of hepatic steatosis in conjunction with at least one cardiometabolic risk factor (CMRF) and no other identifiable cause. Alcohol-associated liver disease, or ALD, is defined as those with excessive alcohol intake greater than 60 g/day. MASLD with mild to moderate alcohol consumption is called MetALD. Individuals with MASLD and steatohepatitis are referred to as metabolic dysfunction-associated steatohepatitis (MASH), a counterpart of the former NASH. SLD with specific etiologies, including drug-induced liver injury and genetic diseases, are listed on the right side. Also, there is cryptogenic SLD, which falls outside of those definitions. The adult criteria for CMRF are as below[5].

At least 1 of the 5 is required:

- BMI ≥ 25 kg/m$^2$ [23 Asia] **OR** WC > 94 cm (M) 80 cm (F) **OR** ethnically adjusted
- Fasting serum glucose ≥5.6 mmol/L [100 mg/dL] **OR** 2-hour post-load glucose levels ≥ 7.8 mmol/L [≥140 mmHg/dL] **OR** HbA1c ≥ 5.7% [39 mmol/L] **OR** type 2 Diabetes **OR** treatment for type 2 diabetes
- Blood pressure ≥ 130/85 mmHg **OR** specific antihypertensive drug treatment
- Plasma Triglyceride ≥ 1.70 mmol/L [150 mg/dL] **OR** lipid-lowering treatment
- Plasma HDL cholesterol ≤1.0 mmol/L [40 mg/dL] (M) and ≤ 1.3 mmol/L [50 mg/dL] (F) **OR** lipid-lowering treatment




Rinella M, et al. A multi-society Delphi consensus statement on new fatty liver disease nomenclature. J Hepatol. 2023 Jun 20;S0168-8278(23)00418-X.

**Figure 3** Steatotic Liver Disease | Subclassification

## Importance of SLD

Figure 4 shows a natural history of SLD, from simple steatosis to steatohepatitis, cirrhosis, and hepatocellular carcinoma. Multiple factors are involved in the progression of steatohepatitis, such as ER stress, oxidative stress, proinflammatory cytokines, and inflammatory macrophages. Decompensated cirrhosis is the end state of NASH or MASH. NASH is now the second leading cause of liver transplantation in the United States, where new registrations on the liver transplant waiting list with NASH have increased 170% from 2004 to 2013[6].

Figure 5 shows the trend of background liver disease in HCC in Japan from a nationwide survey. There was a significant increase in the proportion of patients classified as non-B, non-C, indicated in red, in the participating hospitals. The increase was partly due to a decrease in HCV patients. It is also believed that the rise in obesity over the past three decades has contributed to the increasing number of nonviral patients[7,8]. Based on the nationwide survey, the number of nonviral patients with HCC increased approximately fivefold, from 2,200 in 1992 to 13,000 in 2015. Several regions reported a similar trend.

Not all patients with SLD progress to MASH and liver cirrhosis. The prevalence of MASLD in the general population is 20 to 30%. 10 to 20% of them develop MASH. Among them, 10% will develop liver cirrhosis. Consequently, the annual incidence of MASH-HCC is extremely low at 0.006% in the general population[9].

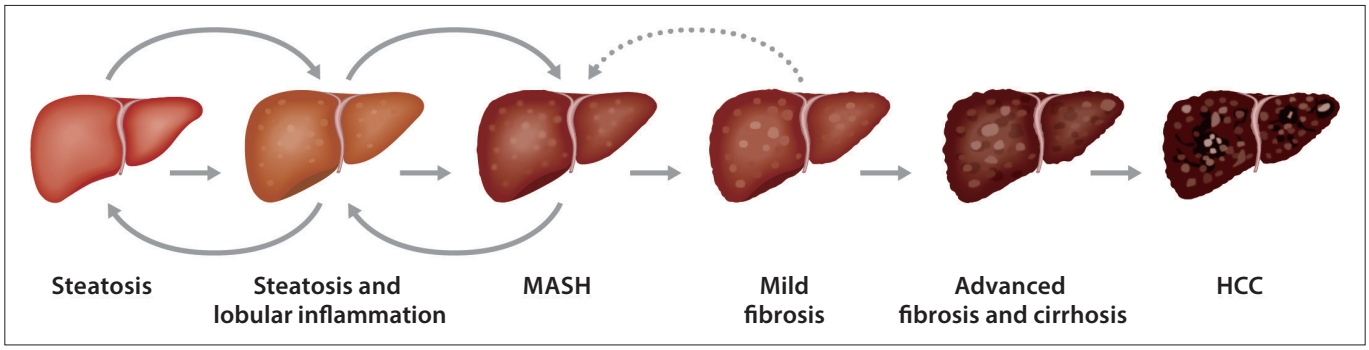



**Figure 4** Progression from Steatosis to Cirrhosis/HCC

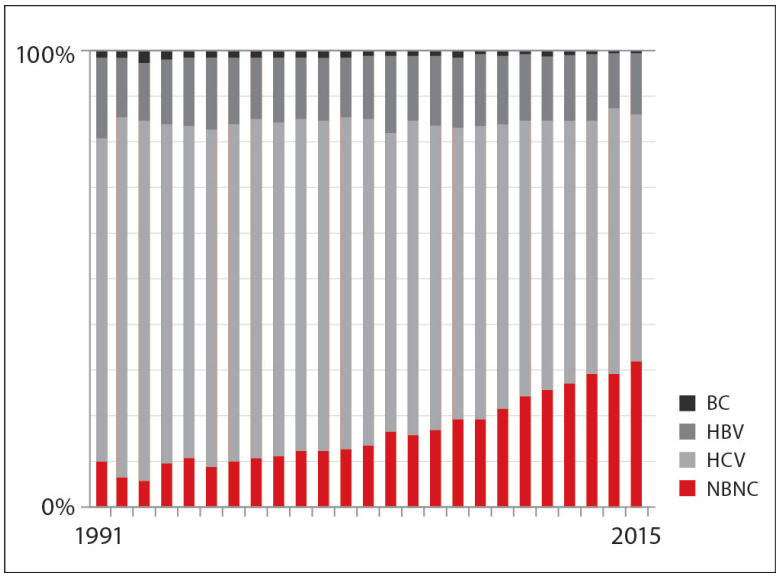



**Figure 5** Trend in etiology of HCC in Japan

Table 1 shows some representative studies of HCC incidence in MASLD and MASH. The upper part in blue indicates cohort studies of MASLD, and the lower part in red indicates hospital-based cohort studies of MASH with advanced fibrosis or cirrhosis.

In a large cohort study in Sweden, the authors enrolled more than 10,000 patients with biopsy-diagnosed NAFLD and selected age and sex-matched control in a ratio of 1 to 5. Then, they collected events from a nationwide registry. The presence of NAFLD increased the risk of all-cause mortality by 11.7 deaths per 1000 person-years. The largest impact was from malignancy from organs other than the liver (+4.5), followed by cirrhosis (+2.6) and cardiovascular disease (+1.4). Although NAFLD increases the risk of cirrhosis-related death and liver cancer-related death by 18.2-fold and 11.1-fold, respectively, the absolute impact on all causes of death was relatively small[10]. On the other hand, the annual HCC incidence exceeds 1.0% in hospital-based studies. Vilar-Gomez and colleagues conducted an international cohort study to enroll biopsy-diagnosed NAFLD with advanced fibrosis (F3) to cirrhosis (F4). The annual incidence in F3 and F4 with the Child-Pugh score of 5 and F4 with that of 6 was 0.3%, 1.8%, and 4.7%, respectively, indicating that the risk of HCC can be further divided even in cirrhosis. The study also showed an inverse relationship between the degree of fat content and the risk of HCC since the steatosis grade generally decreases according to disease progression[11].

| Authors | Object | PY | N | Person-year | HCC | Incidence(%) |
|---|---|---|---|---|---|---|
| Soderberg | MASLD | 2010 | 256 | 5248 | 5 | 0.095 |
| Arase | MASLD | 2012 | 1600 | 13120 | 10 | 0.078 |
| Angulo | MASLD | 2015 | 619 | 7800 | 2 | 0.026 |
| Hägstrom | MASLD | 2017 | 646 | 12631 | 12 | 0.09 |
| Simon | MASLD | 2020 | 10568 | 150065 | 186 | 0.12 |
| Sanyal | MASH | 2006 | 149 | 384 | 10 | 2.6 |
| Yatsuji | MASH-LC | 2009 | 68 | 231 | 8 | 3.4 |
| Ascha | MASH-LC | 2010 | 195 | 624 | 25 | 4.0 |
| Vilar-Gomez | MASH (F3,4) | 2018 | 458 | 2519 | 30 | 1.2 |

**Table 1** HCC from NAFLD/NASH

## Strategy for SLD with significant risk

As described above, it is crucial to find patients with significant risk among the MASLD population. Ultrasound is the mainstay of the screening and diagnosis of SLD. According to the EASL guidelines, ultrasound is recognized as the first-line modality for the diagnosis of MASLD. Figure 6 shows the diagram to screen MASLD. Those with metabolic risk factors undergo ultrasound, and those with abnormal liver enzymes or significant risk factors undergo further investigation[12].

Figure 7a shows representative images of normal, mild to moderate and severe steatosis taken by the Canon Aplio i800. The ultrasound equipment can evaluate the amount of fat content in the liver. As the grade of steatosis increases, the Attenuation Imaging (ATI) value increases from 0.57 in the liver without steatosis to 1.00 in severe steatosis.

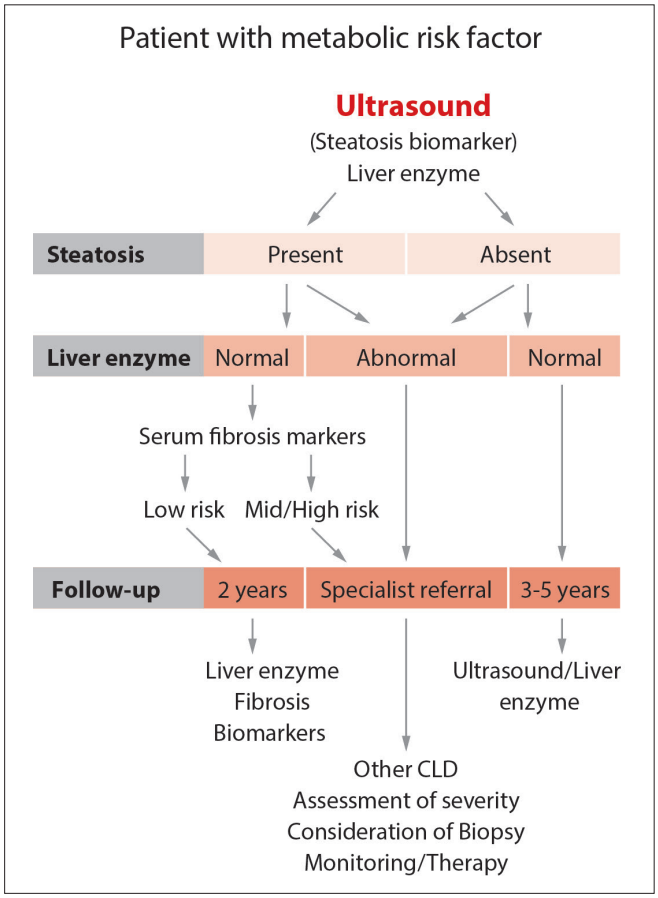



**Figure 6** How to screen MASLD

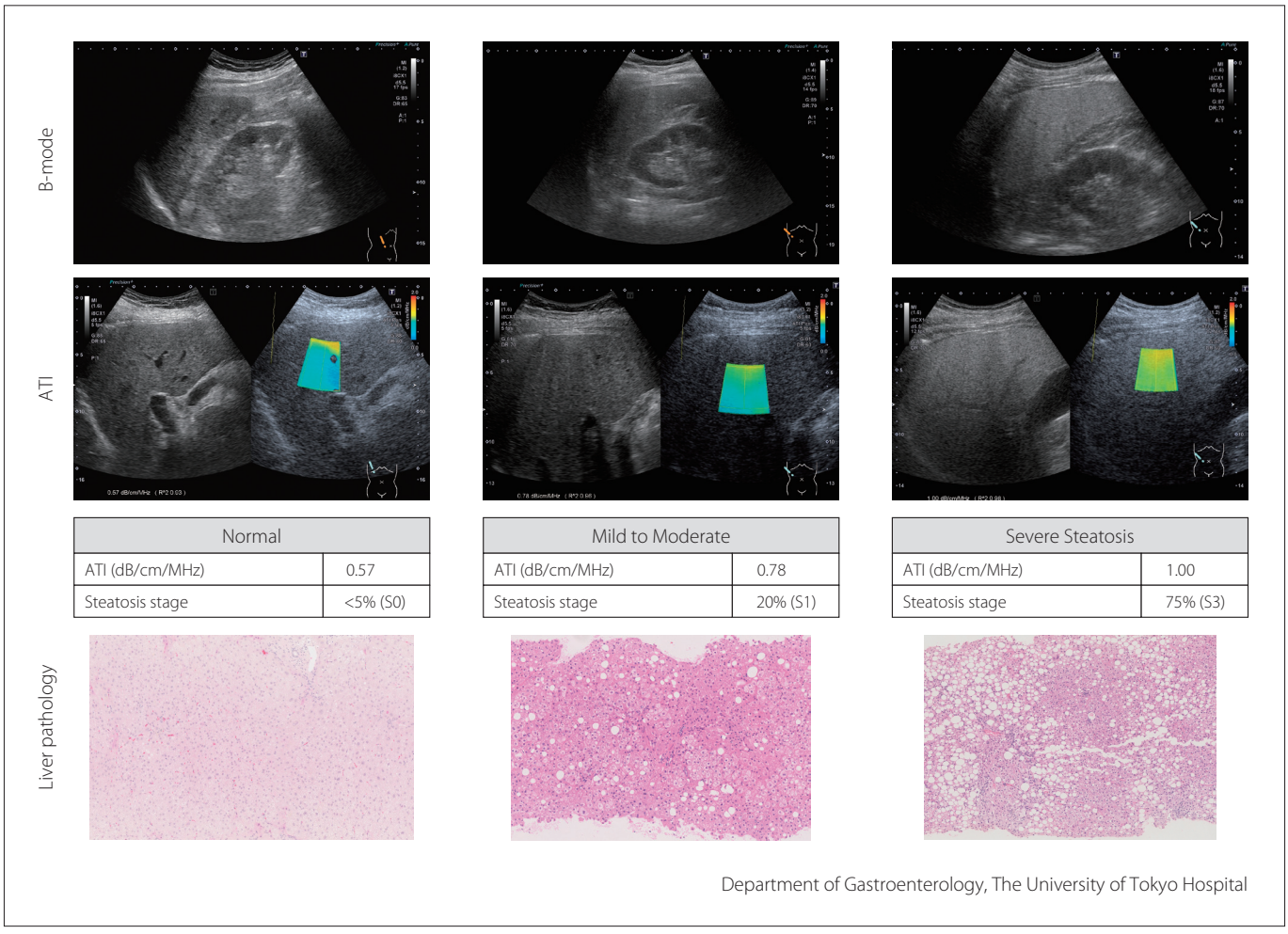
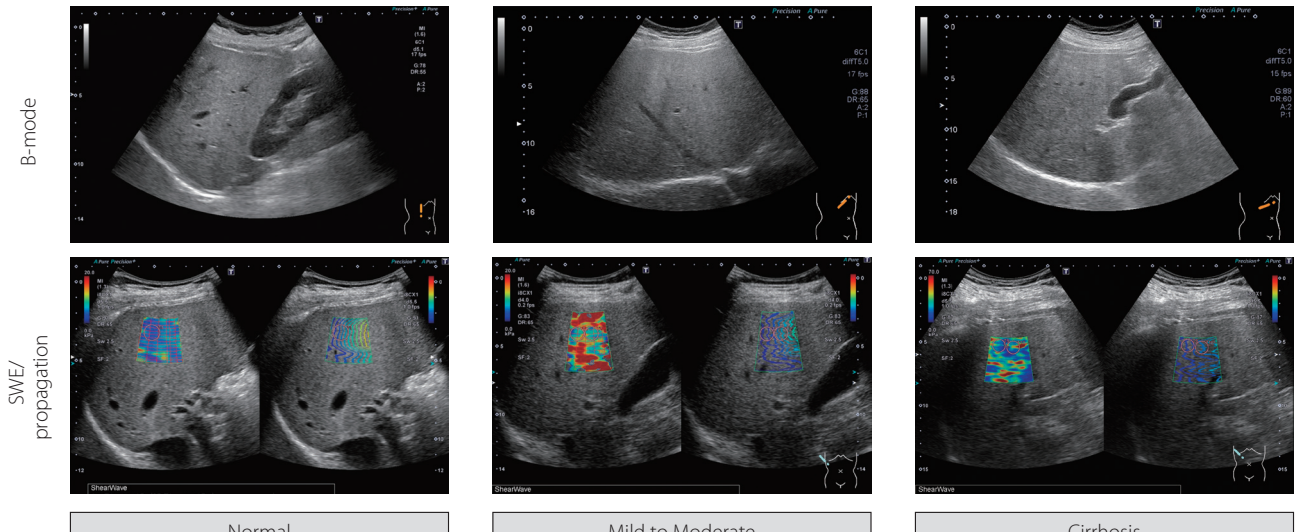



**Figure 7a** Steatosis progression

As described before, the fibrosis stage is the most critical predictor of liver-related complications, including decompensation and hepatocellular carcinoma development. The Aplio series is also equipped with fibrosis measurement with Shear Wave Elastography (SWE) (Fig. 7b). As liver fibrosis progresses from F0 to F4, liver elasticity increases from 4.6 kPa to 21.7 kPa.

In conclusion, MASLD is an important disease category that predicts both liver-related and unrelated mortality. Ultrasound equipment with ATI and SWE provides a value for screening, diagnosis and staging at-risk MASH.




| Normal | |
|---|---|
| SWE (kPa) | 4.6 |
| Fibrosis stage | F0 |

| Mild to Moderate | |
|---|---|
| SWE (kPa) | 8.9 |
| Fibrosis stage | F2 |

| Cirrhosis | |
|---|---|
| SWE (kPa) | 21.7 |
| Fibrosis stage | F4 |

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**Figure 7b** Fibrosis progression

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https://global.medical.canon/News/Events/ultrasound-webinar-20231116


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The clinical results described in this paper are the experience of the author.
Results may vary due to clinical setting, patient presentation and other factors.

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