

Characteristic Features of Nonalcoholic Fatty Liver Disease in Japan with a Focus on the Roles of Age, Sex and Body Mass Index

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This review provides an update on the characteristics of nonalcoholic fatty liver disease (NAFLD), with a focus on the effects of age, sex, and body mass index. Age is a risk factor for NAFLD progression; however, extremely old patients have unique features, namely, the associations between metabolic comorbidities and NAFLD are weaker and NAFLD is not a risk factor for mortality. The prevalence of NAFLD is higher in men than in premenopausal women, whereas the reverse is true after menopause. Thus, before menopause, estrogen may have protective effects against NAFLD. Our hospital data showed that over 25% of male patients with NAFLD and almost 40% of female patients with NAFLD, especially elderly patients, were nonobese. Although histological steatosis and activity were associated with body mass index, the prevalence of nonalcoholic steatohepatitis was not. The prevalence of advanced fibrosis showed a significant sex difference. Advanced fibrosis was significantly more frequent among severely obese men but the prevalence was lower among severely obese women. This difference could be because a substantial proportion of severely obese women were premenopausal; thus, estrogen may have much stronger effects on the development of fibrosis than on obesity. Further studies are required to develop tailored management strategies. (**Gut Liver 2020;14:537-545**)

Key Words: Non-alcoholic fatty liver disease; Age, sex difference; Lean NAFLD; Obesity; Body mass index

INTRODUCTION

The obesity pandemic has become a major public health problem and has resulted in a dramatic increase of metabolic syndrome, type 2 diabetes, hyperlipidemia, hypertension, and

nonalcoholic fatty liver disease (NAFLD). NAFLD can be both the result and cause of metabolic syndrome and these diseases, due to the existence of a vicious cycle linking these conditions. NAFLD encompasses a broad spectrum of hepatic injury that ranges from simple steatosis (nonalcoholic fatty liver [NAFL]) to steatohepatitis (nonalcoholic steatohepatitis [NASH]). NAFL is generally benign and non-progressive, while NASH can progress to cirrhosis and even hepatocellular carcinoma (HCC). Currently, NAFLD is the leading cause of chronic liver disease worldwide, as well as the most rapidly increasing cause of cirrhosis and HCC.¹⁻⁸ Individuals with NAFLD have a higher standardized mortality ratio (hazard ratio of around 1.6) compared with the general population due to elevation of both liver-related and cardiovascular mortality.⁹⁻¹⁷ The most common causes of death among NAFLD patients are malignancy or cardiovascular disease, followed by liver-related disease. It is thought that NAFLD generally shows slow progression, with liver-related morbidity and mortality occurring in a small proportion of patients. A strong association of the prevalence and severity of NAFLD with age, sex, and ethnicity is well known.^{1-5,18,19}

Obesity is a major determinant of the prevalence of NAFLD.¹⁻⁵ Previous studies have clearly demonstrated that Asian populations have a higher risk of insulin resistance, type 2 diabetes, NAFLD/NASH, and cardiovascular disease than populations of European descent at any given body mass index (BMI).²⁰ This difference in the level of risk may be explained by the presence of more visceral fat and subcutaneous fat in Asians than in Europeans at any given BMI, as well as earlier arrest of adipocyte maturation and development of insulin resistance in Asians during weight gain.²¹⁻²⁴ Based on these considerations, obesity is defined as a BMI ≥ 25 kg/m² for the Japanese population instead of a BMI ≥ 30 kg/m², as it is for Europeans.²⁵ The severity of obesity in a population parallels the incidence of NAFLD. How-

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ever, occurrence of NAFLD in lean or nonobese individuals has also been attracting attention, because lean NAFLD is not rare and is generally not a benign condition.^{26,27}

This review provides an update on the characteristics of NAFLD/NASH, focusing on the influence of age, sex, and BMI.

EPIDEMIOLOGY

A very large meta-analysis (8,515,431 subjects from 22 countries) performed by Younossi *et al.*¹⁵ showed that the global prevalence of NAFLD among adults is 25.24% (95% confidence interval [CI], 22.10 to 28.65), with the highest prevalence being found in the Middle East (31.79%), followed by South America (30.45%) and Asia (27.37%). The higher prevalence of NAFLD in these geographic areas seems to be mainly explained by genetic factors. A single nucleotide polymorphism of patatin-like phospholipase domain-containing protein 3 (*PNPLA3*) rs738409 is known to be the most important risk allele for the onset and progression of NAFLD, as well as for development of HCC, with the G allele increasing the risk of these outcomes.²⁸⁻³⁰ The *PNPLA3* risk allele is most common among Hispanics, who show the highest susceptibility to NAFLD, followed by Asians, and it is more frequent in nonobese NAFLD patients.³¹ NAFLD is associated with various metabolic comorbidities, including obesity (51.34%; 95% CI, 41.38 to 61.20), type 2 diabetes (22.51%; 95% CI, 17.92 to 27.89), hyperlipidemia (69.16%; 95% CI, 49.91 to 83.46), hypertension (39.34%; 95% CI, 33.15 to 45.88), and metabolic syndrome (42.54%; 95% CI, 30.06 to 56.05).

According to data obtained from annual health check, the prevalence of NAFLD in Japan is estimated to be around 10% to 30%,^{1,32-34} suggesting that the prevalence of NASH may fall within the range of 2% to 6%. The prevalence of NAFLD generally increases with BMI, being 5% to 20% in nonobese individuals, around 50% in persons with a BMI exceeding 25 kg/m² and less than 30 kg/m², and around 80% in those with a BMI over 30 kg/m². It has been reported that the prevalence of NAFLD is around 50% in patients with type 2 diabetes and 40% among those with dyslipidemia. Obesity and metabolic comorbidities have a synergistic effect on the incidence of NAFLD.

Surveys on the etiology of liver cirrhosis and HCC in Japan have shown that hepatitis C virus infection is the leading cause of HCC (53%), followed by hepatitis B (13%) virus infection, while NAFLD accounts for 5.8% of cirrhosis and 4.3% of HCC.^{35,36} There is no doubt that NAFLD will increase in the future.

There has been an increase of reports about HCC in patients with NAFLD/NASH.³⁷⁻⁴⁸ As with other liver diseases, the most important risk factors for HCC are cirrhosis, age and male sex. In addition, obesity, type 2 diabetes, and *PNPLA3* increase the risk of HCC. Their mean age at diagnosis of HCC is around 70 years old and they show male predominance. In comparison with patients whose HCC is due to other etiologies, patients with

NAFLD/NASH-related HCC are more likely to have comorbidities such as obesity, type 2 diabetes, hypertension, and cardiovascular disease. The most problematic aspect of NAFLD/NASH-related HCC is development of a substantial number of tumors in patients without cirrhosis.

Hepatitis B virus infection is the predominant etiology of HCC in Korea as well as in China and Taiwan. HCC cases from etiologies other than viral hepatitis infection, or alcohol ranged from 6.8% to 15.1%. NAFLD-related HCC falls in this category. Since Korea is a hepatitis B virus-endemic area, prior hepatitis B virus infection is considered to play a role even in the development of NAFLD-related HCC.⁴⁹

In the United States, NAFLD has been recognized as one of the leading causes of cirrhosis in adults and NAFLD-related cirrhosis is currently the second most frequent indication for liver transplantation.^{5,15,50,51}

AGE

The most important histological feature of NAFLD/NASH associated with mortality is the severity of fibrosis.^{14,52-54} Risk factors for the development of advanced fibrosis or cirrhosis are reported to be age, type 2 diabetes, morbid obesity, *PNPLA3* and elevation of transaminases.⁵⁵⁻⁶² Fig. 1 is a distribution of NAFLD patients diagnosed at our university hospital by age and sex from severity of fibrosis. In older generation advanced fibrosis was more common than mild fibrosis in both genders. Aging is associated with multidimensional functional decline. The age-associated decline of mitochondrial function and antioxidant mechanisms contributes to development of metabolic syndrome and metabolic comorbidities.⁶³ Aging also affects liver morphology and physiology, with nearly one third of hepatic volume and perfusion being lost between the ages of 30 and 100 years.⁶⁴ Histological examination reveals enlargement of hepatocytes, an increase of binucleated hepatocytes, and a decrease of mitochondria with aging.^{65,66} Age is also a risk factor for hepatic steatosis due to the onset of multiple abnormalities of hepatic lipid metabolism. A gradual decline in the production of sex hormones, growth hormone, and insulin-like growth factor 1 with aging might be one reason for development of hepatic steatosis.⁶⁷ In addition, older age is associated with reduced physical activity, which leads to sarcopenia, that is, a decrease of muscle mass and function. Recent studies have shown that sarcopenia is a risk factor for the development and progression of NAFLD independently of obesity, insulin resistance, and metabolic syndrome.⁶⁸⁻⁷⁰ All of these factors may contribute to the increasing prevalence and severity of metabolic syndrome and NAFLD/NASH with advancing age.

We previously analyzed the influence of age, sex, and lifestyle-related diseases in 193 patients with biopsy-proven NASH.⁵⁷ To assess the effect of menopause, we separated the patients into groups younger and older than 55 years. Women

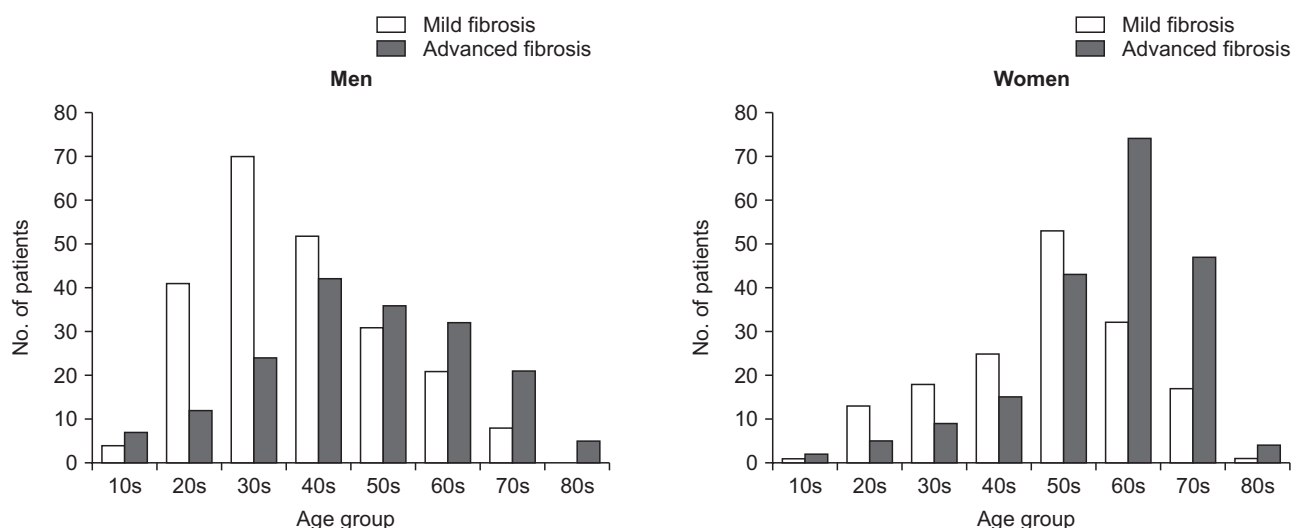


Fig. 1. Distribution of patients with nonalcoholic fatty liver disease by mild or advanced fibrosis status with respect to age and sex. In the older generation, advanced fibrosis was more common than mild fibrosis in both sexes. Data was obtained from Tokyo Women's Medical University in 1991 to 2018 (n=811: 406 men and 359 women).

were predominant in the older group (23.8% in the younger group vs 67.4% in the older group, $p < 0.001$). The prevalence of severe obesity (defined as a BMI $> 30 \text{ kg/m}^2$) and hyperlipidemia was higher in the younger group (36.6% vs 16.3%, $p = 0.002$ and 73.3% vs 50.5%, $p = 0.001$, respectively). In contrast, type 2 diabetes and hypertension were significantly more common in the older group (30.7% vs 53.3%, $p = 0.001$ and 14.9% vs 45.7%, $p < 0.001$, respectively). Liver biopsy showed that the older group had a significantly higher prevalence of advanced fibrosis (23.8% vs 54.3%, $p < 0.001$). Multivariate analysis of risk factors for advanced fibrosis revealed that age (odds ratio, 1.089; 95% CI, 1.024 to 1.159) and BMI (odds ratio, 1.101; 95% CI, 1.011 to 1.199) were independent predictors in the younger group. In contrast, absence of hyperlipidemia (odds ratio, 0.389; 95% CI, 0.157 to 0.966) was the only significant independent predictor of advanced fibrosis in the older group. Our study showed that NASH was infrequent among young women, while women (probably postmenopausal) were predominant among the subjects older than 55 years. The metabolic comorbidities associated with NASH differed with age, since a higher prevalence of severe obesity and hyperlipidemia was noted in the younger group, while type 2 diabetes and hypertension were more frequent in the older group. Advanced liver fibrosis showed an increase with aging, while age and BMI (younger group) or the absence of hyperlipidemia (older group) were predictors for advanced fibrosis. These results are consistent with other reports.

However, the situation is completely different among very old patients with NAFLD. Kagansky *et al.*⁷¹ evaluated 91 octogenarians admitted to the rehabilitation department of a geriatric hospital and found NAFLD (diagnosed by ultrasonography criteria) in 42 of them (46.2%). There were no significant differences of the following parameters between the patients with or without

NAFLD: age, sex, chronic illnesses, anthropometric parameters, lipid profile, fasting glucose, prevalence of metabolic syndrome, and the levels of transaminases, ferritin, and iron. Conversely, NAFLD patients younger than 70 years had a significantly higher prevalence of obesity, glucose intolerance, and metabolic syndrome compared with the elderly NAFLD patients. According to a population-based study of 2,811 participants (mean age: 76.4 ± 6.0 years) performed in Rotterdam, the prevalence of NAFLD diagnosed by ultrasonography decreased with advancing age ($p < 0.001$), declining from 35.8% among participants < 70 years old to 21.1% among those aged ≥ 85 years.⁷² Similarly the association between metabolic syndrome and NAFLD became weaker with advancing age.

Golabi *et al.*⁷³ assessed the prevalence, risk factors, and mortality of NAFLD in 3,271 individuals older than 60 years by using data from the Third National Health and Nutrition Examination Survey linked with mortality information. They reported that the prevalence rate of NAFLD was 40.3% among subjects aged 60 to 74 years and 39.2% among those aged > 74 years. Among the subjects aged 60 to 74 years, the risk of 5-year all-cause mortality was associated with the presence of NAFLD (adjusted hazard ratio, 1.60; 95% CI, 1.24 to 1.96) and cardiovascular mortality was also higher in this group. In contrast, NAFLD was not associated with all-cause mortality or cardiovascular mortality among individuals aged > 74 years.

According to our nationwide survey of HCC due to nonviral chronic liver disease in Japan, most HCC patients aged 80 years or older did not have any known etiology, such as alcoholic liver disease or NAFLD, and their condition was classified as cryptogenic (Fig. 2).⁴¹ Among HCC patients aged 80 years or older, the prevalence of obesity, type 2 diabetes, and cirrhosis was also significantly lower than in younger patients. These findings were

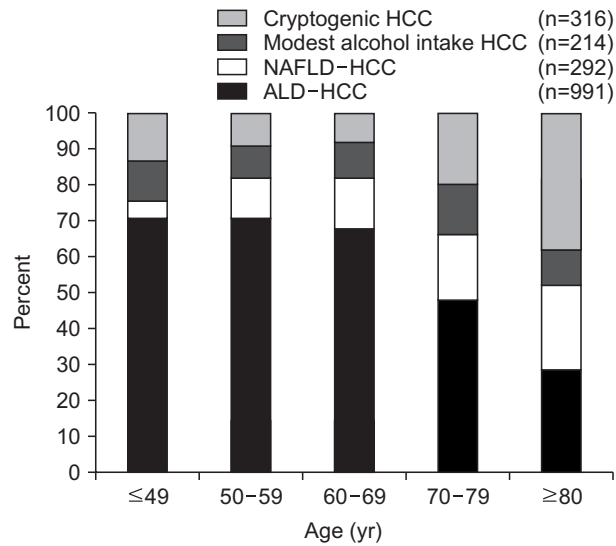


Fig. 2. Etiology of nonviral hepatocellular carcinoma (HCC) with respect to age based on a nationwide survey in 2009.⁴¹ Among patients aged over 80 years, the percentage of cryptogenic HCC was increasing, and the prevalence of obesity, type 2 diabetes, and cirrhosis was significantly lower in this patient group. NAFLD, nonalcoholic fatty liver disease; ALD, alcoholic liver disease.

similar to those for NAFLD patients in the same age groups.

Thus, the association between metabolic comorbidities and NAFLD becomes weaker in the very old population. In addition, NAFLD is not associated with an increased risk of mortality in this age group. The age defined as “elderly” varies among studies and this may lead to conflicting results.

GENDER DIFFERENCE

As we mentioned, the prevalence of NAFLD is higher in men than in premenopausal women, while the reverse is true after menopause.^{8,18,19,32,34,74-79} This difference has generally been explained by the influence of sex hormones. Estrogen regulates energy homeostasis by controlling mitochondrial structure and function, as well as by enhancing insulin release and modulating the secretion/action of growth hormone.⁸⁰ Postmenopausal women tend to gain weight along with a shift in its distribution to an increase of visceral fat.⁸¹⁻⁸⁵ Most women reach their maximum body weight after menopause. Experimental studies have shown that estrogen decreases the generation of reactive oxygen species, down-regulates the expression of transforming growth factor beta-1, and inhibits activation and fibrogenesis by stellate cells.^{86,87} Accordingly, women are protected from the development and progression of NAFLD/NASH by estrogen before menopause. In addition, it has been reported that hormone replacement therapy has a protective effect against metabolic syndrome and NAFLD after menopause.⁸⁸ Recent studies have demonstrated that testosterone is also closely associated with metabolic syndrome, type 2 diabetes, and NAFLD.⁸⁹⁻⁹⁴ Production of testosterone gradually decreases with aging, and the

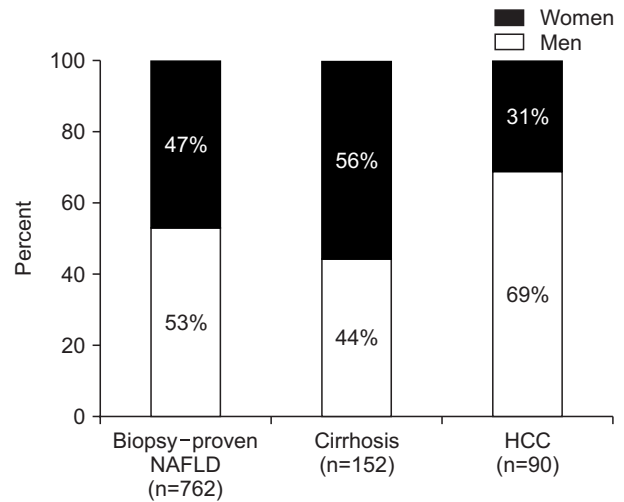


Fig. 3. Percentage of male and female patients with a diagnosis of nonalcoholic fatty liver disease (NAFLD), cirrhosis, or hepatocellular carcinoma (HCC). Our hospital data showed a male predominance in all patients with NAFLD, although a female predominance was noted in patients with cirrhosis. A male predominance was noted in patients with HCC.

prevalence of these diseases increases at an older age.

According to data from annual health checks performed in Japan, the prevalence of NAFLD among men is around 30% in all age groups above 30 years old.³² In contrast, it gradually increases from 7% among women in their 30s to 23% for women above 60 years old. In a series of 762 patients with biopsy-proven NAFLD diagnosed at our university hospital, males were predominant. The percentage of cirrhotic NAFLD was higher in women than in men (56% vs 44%), while the percentage of HCC was higher in men than in women (69% vs 31%) (Fig. 3). This difference in cirrhosis is probably due to the women being about 10 years older than men. As we mentioned, age is a risk factor for progression of fibrosis. The gender difference of HCC may be partly attributable to differences in exposure to the risk factors for this cancer, such as less alcohol consumption and smoking among women.^{37,95,96} However, it was reported that estrogen-mediated inhibition of interleukin 6 production explained the gender disparity of HCC in mouse models,⁹⁷ so estrogen may also influence the pathogenesis of human HCC.

Yang *et al.*⁹⁸ performed a cross-sectional study that investigated the influence of sex and menopause on the severity of liver fibrosis using a large single-center prospective database of 541 patients with a histologic diagnosis of NASH. After adjusting for covariates, the adjusted cumulative odd ratio for more severe fibrosis was 1.4 (95% CI, 0.9 to 2.1; $p=0.17$) among postmenopausal women and 1.6 (95% CI, 1.0 to 2.5; $p=0.03$) among men, using premenopausal women as the reference. Thus, they found that men had a higher risk of more severe fibrosis compared to women before menopause, while the severity of liver fibrosis was similar between postmenopausal women and men.

However, our data showed that sex had no influence on the

severity of fibrosis when NASH patients were classified into younger or older groups for multivariate analysis.⁵⁷ In fact, recent our data of NAFLD patients showed that advanced fibrosis in 36% of 284 younger men and 31% of 132 younger women, while advanced fibrosis existed in 64% of 120 older men and 63% of 226 older women (Fig. 4) These were very similar frequencies for both sexes. Therefore, further studies are needed to better understand the influence of sex on progression of fibrosis in NAFLD/NASH.

LEAN NAFLD

The prevalence of lean NAFLD varies due to differences in the definition of lean or nonobese NAFLD and differences in

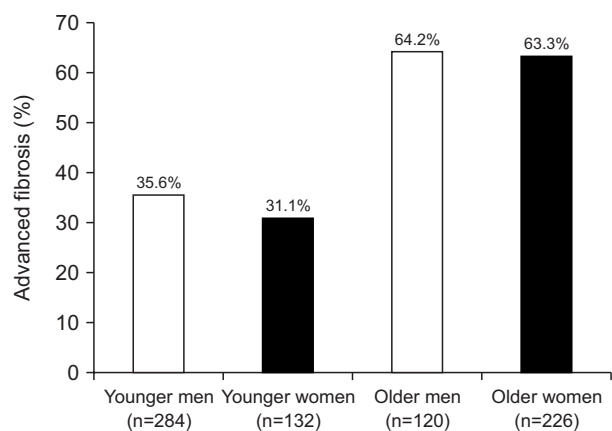


Fig. 4. Percentage of nonalcoholic fatty liver disease patients with advanced fibrosis in the younger and older groups with respect to sex. The frequencies for both sexes were similar.

the method of diagnosis (imaging modalities or histology), with the reported prevalence ranging from approximately 10% to 30%.^{26,27,99-104} Previous studies have shown that patients with lean NAFLD usually have insulin resistance and higher plasma triglyceride levels compared to matched controls without NAFLD, although both of these changes are usually smaller than in patients with obese NAFLD. Histologically the prevalence of NASH and the severity of fibrosis do not differ significantly between nonobese and obese patients with NAFLD, but nonobese NAFLD patients have less severe steatosis. Unfortunately, no analyses stratified by sex were done in these studies, despite the features of NAFLD/NASH showing gender differences as mentioned above.

To investigate the features of male and female patients with nonobese NAFLD, we performed a cross-sectional single-center study of 762 patients with biopsy-proven NAFLD.²⁷ The patients were classified into three groups according to the Japanese criteria for obesity, which were a nonobese group (BMI <25 kg/m²), an obese group (25 to 30 kg/m²), and a severely obese group (≥30 kg/m²).

We found that 28.7% of the men and 39.1% of the women had nonobese NAFLD. The percentage of nonobese, obese and severely obese NAFLD patients clearly showed that severely obese patients were more common in the younger generation and nonobese patients were more common in the older generation in both genders (Fig. 5). Visceral fat obesity measured by computed tomography was found in 80% of the male patients and 87% of the female patients with nonobese NAFLD. Only 1.9% of male NAFLD patients and 0.6% of female NAFLD patients had no risk factors for NAFLD. The median age of the nonobese, obese, and severely obese men was 49.9 years, 46.8

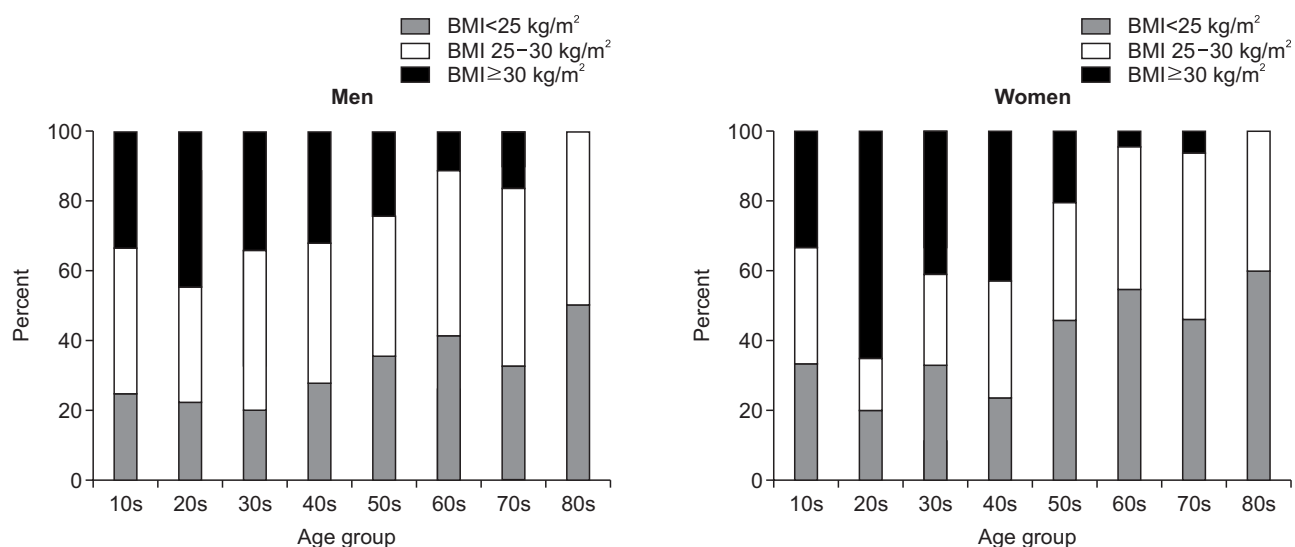


Fig. 5. Percentage of nonobese, obese, and severely obese patients with nonalcoholic fatty liver disease with respect to age and sex.²⁷ For both sexes, severely obese patients were more common in the younger generation, and nonobese patients were more common in the older generation. Data was obtained from Tokyo Women's Medical University in 1991 to 2018 (n=762). BMI, body mass index.

years, and 40.5 years ($p < 0.01$), respectively, while the women were aged 60.2 years, 59.6 years, and 48.5 years ($p < 0.01$), respectively. Interestingly, the prevalence of metabolic comorbidities and *PNPLA3* risk alleles did not differ among the three BMI groups in both genders. Also, the prevalence of NASH did not differ significantly among these groups, although nonobese patients of both sexes were more likely to have mild steatosis and low histological activity. Most of these findings were consistent with previous reports.^{26,99-103} Surprisingly, the prevalence of advanced fibrosis showed a marked difference between men and women. In men, advanced fibrosis was significantly more common among severely obese NAFLD patients (nonobese, 31.0%; obese, 41.6%; severely obese, 60.9%; $p < 0.01$), even though the severely obese group was the youngest. However, the opposite was seen in women, and the prevalence of advanced fibrosis was significantly lower in severely obese female NAFLD patients than in obese or nonobese patients (nonobese, 51.4%; obese, 62.9%; severely obese, 33.7%; $p < 0.01$). As in men, the severely obese group was youngest among women. Thus, obesity was associated with advanced liver fibrosis in men, but not in women. This difference may have arisen because a substantial proportion of severely obese women were premenopausal, and suggests that estrogen may have a much stronger influence on the development of fibrosis than obesity among females.

The nonobese group was the oldest of the three groups among both men and women. It is well known that elderly persons lose muscle mass (sarcopenia) and gain weight due to accumulation of fat. We clearly showed that the limb skeletal muscle mass and skeletal muscle index (skeletal muscle mass of the four limbs/height² [kg/m²]) were lower in patients with non-obese NAFLD, suggesting that sarcopenia may be a risk factor for NAFLD among nonobese persons.

NAFLD/NASH occurred in nonobese subjects, especially in elderly persons, and was not milder than in obese subjects. While histological steatosis and activity were associated with BMI, the prevalence of NASH and advanced fibrosis were not. Prevalence of advanced fibrosis showed a significant sex difference.

CONCLUSION

Age and sex are important determinants of the clinical characteristics of NAFLD/NASH. Because the factors contributing to development and progression of NAFLD are complex, further large-scale studies of patients stratified by age, sex, ethnicity, and genetic status will be required to elucidate its pathogenesis and clinical features, in order to develop evidence-based tailored management strategies.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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