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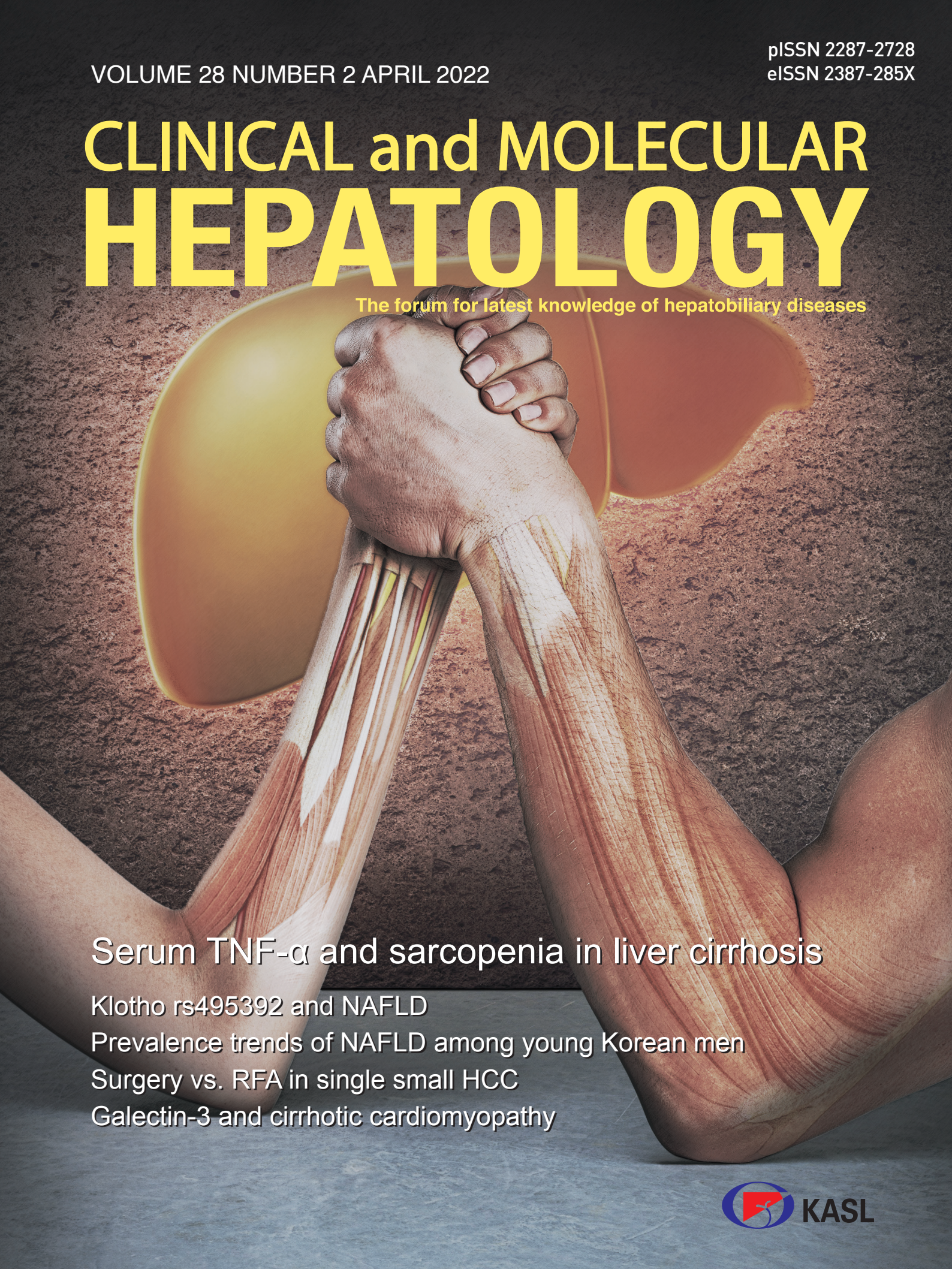

Serum TNF-α and sarcopenia in liver cirrhosis

Klotho rs495392 and NAFLD
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Review

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MAFLD enhances clinical practice for liver disease in the Asia-Pacific region

Takumi Kawaguchi[1], Tsubasa Tsutsumi[1], Dan Nakano[1], Mohammed Eslam[2], Jacob George[2], and Takuji Torimura[1]

[1]Division of Gastroenterology, Department of Medicine, Kurume University School of Medicine, Kurume, Japan; [2]Storr Liver Centre, Westmead Institute for Medical Research, Westmead Hospital and University of Sydney, New South Wales, Australia

Fatty liver is now a major cause of liver disease in the Asia-Pacific region. Liver diseases in this region have distinctive characteristics. First, fatty liver is frequently observed in lean/normal-weight individuals. However, there is no standard definition of this unique phenotype. Second, fatty liver is often observed in patients with concomitant viral hepatitis. The exclusion of viral hepatitis from non-alcoholic fatty liver disease limits its value and detracts from the investigation and holistic management of coexisting fatty liver in patients with viral hepatitis. Third, fatty liver-associated hepatocellular carcinoma (HCC) is generally categorized as non-B non-C HCC. Fourth, the population is aging rapidly, and it is imperative to develop a practicable, low-intensity exercise program for elderly patients. Fifth, most patients and non-specialized healthcare professionals still lack an awareness of the significance of fatty liver both in terms of intrahepatic and extrahepatic disease and cancer. Recently, an international expert panel proposed a new definition of fatty liver: metabolic dysfunction-associated fatty liver disease (MAFLD). One feature of MAFLD is that metabolic dysfunction is a prerequisite for diagnosis. Pertinent to regional issues, MAFLD also provides its diagnostic criteria in lean/normal-weight individuals. Furthermore, MAFLD is independent of any concomitant liver disease, including viral hepatitis. Therefore, MAFLD may be a more suitable definition for fatty liver in the Asia-Pacific region. In this review, we introduce the regional characteristics of fatty liver and discuss the advantages of MAFLD for improving clinical practice for liver disease in the region. **(Clin Mol Hepatol 2022;28:150-163)**

Keywords: Fatty liver; Leanness; Hepatitis viruses; Liver cancer; Awareness

INTRODUCTION

Liver disease is highly prevalent in the Asia-Pacific region, accounting for over 60% of global liver-related deaths.[1,2] The main causes of liver-related mortality are liver cirrhosis and liver cancer. The Asia-Pacific region accounts for approximately half of deaths due to cirrhosis and three-quarters of deaths due to liver cancer globally.[1] Thus, treatment of liver disease should be a focus for improving health in the Asia-Pacific region.[3-5]

During the past four decades, great progress has been made in the prevention and treatment of viral hepatitis.[6] Universal infant hepatitis B virus (HBV) vaccination has significantly reduced the prevalence of hepatitis B virus surface antigen (HBsAg).[7] Nucleos(t)ide analogs suppress HBV replication and increase the rate of HBsAg seroclearance with favorable clinical outcomes, including a reduction in the incidence of hepatocellular carcinoma

Abbreviations:

ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CH-B, chronic hepatitis B; CI, confidence interval; DAAs, direct-acting antivirals; HBsAg, hepatitis B virus surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; MAFLD, metabolic dysfunction-associated fatty liver disease; miR, micro RNA; NAFLD, non-alcoholic fatty liver disease; OR, odds ratio

Corresponding author : Takumi Kawaguchi
Division of Gastroenterology, Department of Medicine, Kurume University School of Medicine, 67 Asahi-machi, Kurume 830-0011, Japan
Tel: +81-942-31-7627, Fax: +81-942-31-2623
E-mail: takumi@med.kurume-u.ac.jp
https://orcid.org/0000-0002-7064-4325

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(HCC).[8] Likewise, the nucleic acid test for hepatitis C virus (HCV) has contributed tremendously to the prevention of transfusion transmission,[9] while all-oral direct-acting antivirals (DAAs) for HCV have resulted in high cure rates in Asia-Pacific patients in general clinical practice settings, including elderly patients and those with decompensated cirrhosis.[10] The World Health Organization published the Global Health Sector Strategy on viral hepatitis and aims to eliminate viral hepatitis by 2030 by reducing new viral hepatitis infections and reducing deaths due to viral hepatitis.[11] As a result, the prevalence of viral hepatitis is expected to rapidly decrease in the Asia-Pacific region.

Concomitantly, a rapid increase has been observed in the prevalence of fatty liver disease, estimated at approximately 30% of the Asia-Pacific population.[12-17] Consequently, fatty liver is both a major etiology of chronic liver disease and will be an increasing cause of liver-related death in the future.[13,18] As in Western countries, obesity and type 2 diabetes mellitus are the dominant risk factors for clinical progression and adverse outcomes in patients with fatty liver disease in the Asia-Pacific region.[19-22]

Fatty liver in this region also has distinctive features. First, non-obese fatty liver accounts for approximately 40% of cases of fatty liver.[23] While metabolic dysfunction is associated with the development of fatty liver in non-obese individuals,[24,25] there are no standardized diagnostic criteria. Second, fatty liver is often seen in patients with viral hepatitis.[26,27] However, the exclusion of viral hepatitis from non-alcoholic fatty liver disease (NAFLD) limits the investigation of any coexisting fatty liver, while also reducing awareness both at the patient and clinician levels. Third, with regard to HCC, fatty liver disease is generally categorized as non-B non-C or non-viral HCC.[28-31] Therefore, precise information and therapeutic strategies are still lacking for this entity. Fourth, rapid population aging is seen in the Asia-Pacific region,[32,33] and it is important to develop a practical, low-intensity exercise program that is suitable even for elderly patients with poor cardiorespiratory fitness. Fifth, most patients and non-specialized healthcare professionals remain unaware of the significance of fatty liver disease.[34,35] This lack of awareness has significant negative impacts on lifestyle intervention, patient-reported outcomes, and the economic burden on patients and healthcare systems. We contend that the diagnostic term used for fatty liver should be based on these regional characteristics.

METABOLIC DYSFUNCTION-ASSOCIATED FATTY LIVER DISEASE (MAFLD)

Recently, an international expert panel proposed a new definition of fatty liver disease, MAFLD.[36] MAFLD is not simply a renaming of NAFLD but represents a new concept for understanding liver disease related to metabolic dysregulation.[37] A diagnosis of MAFLD is made based on evidence of fatty liver in patients who are overweight/obese or have type 2 diabetes mellitus. In addition, MAFLD can be diagnosed in lean/normal-weight people with the criteria requiring evidence of fatty liver and at least two metabolic abnormalities.[36] The prevalence of MAFLD is approximately 80% in patients with fatty liver and 30% to 40% of the general population in Asia.[38-41]

According to the new criteria, the MAFLD definition excludes patients with fatty liver and no metabolic abnormalities, with the corollary result of its predictive ability for clinical events being higher for MAFLD than for NAFLD. In fact, in contrast to NAFLD, MAFLD better identifies patients with hepatic fibrosis, a high risk of atherosclerotic cardiovascular disease (ASCVD), chronic kidney disease, colorectal polyps, and all-cause mortality.[40-48] Another important distinction is that MAFLD is independent of alcoholic intake or other liver diseases, including viral hepatitis. Therefore, patients with dual (or more) etiologies of liver disease can be diagnosed with "MAFLD and alcoholic liver disease" or "MAFLD and chronic hepatitis B (CH-B)."[49,50] Therefore, MAFLD allows us to investigate the impact of coexisting fatty liver in patients with viral hepatitis. Such assessments will also impact studies of viral hepatitis and MAFLD in their contribution to HCC development.

VALIDITY OF THE MAFLD DEFINITION FOR PEOPLE WHO ARE LEAN/NORMAL WEIGHT

Patients with fatty liver who are a healthy weight are often metabolically unhealthy. Several studies have reported that the incidence of advanced fibrosis and liver-related events in these patients is similar to or worse than that in patients with fatty liver who are overweight/obese.[51-53] In addition, a higher risk for ASCVD and higher all-cause mortality has been reported in patients with fatty liver in the context of normal weight than that in patients who are overweight/obese.[53-55]

Patients with lean/normal weight fatty liver have been reported to progress to advanced liver disease, ASCVD, and liver-related mortality, independent of PNPLA3 genotype.[56] No significant dif-

ference has been reported in the prevalence of visceral adiposity, hypertension, and dyslipidemia between patients with lean/normal weight and those with overweight/obese fatty liver.[57,58] Metabolic syndrome has been reported to be associated with the development of advanced hepatic fibrosis in patients with lean/normal weight fatty liver.[24,25] Recently, Francque and Wong[59] noted that metabolic dysfunction may be the main risk factor that is associated with an increased risk of hepatic fibrosis among lean patients with MAFLD. Park et al.[60] also reported that diabetes mellitus is the strongest risk factor for hepatic fibrosis in lean patients. Furthermore, lifestyle intervention is effective for these patients.[61,62] These previous findings suggest that various metabolic abnormalities may be involved in the development and progression of fatty liver in lean/normal-weight individuals.

The international expert panel proposed a definition of lean/normal weight MAFLD in Asian patients (body mass index [BMI] <23 kg/m^2), which requires the presence of fatty liver with a combination of at least two of the following metabolic abnormalities: visceral adiposity, hypertension, dyslipidemia, pre-diabetes, insulin resistance, or an elevation of serum high-sensitivity C-reactive protein level (Fig. 1).[36] The prevalence of lean/normal weight MAFLD has been reported to be 16% to 18% of patients with MAFLD in the Asia-Pacific region.[40,63]

Several studies have used the lean/normal-weight MAFLD definition. Ciardullo et al.[64] demonstrated that a high prevalence of significant fibrosis is seen in patients with lean/normal-weight MAFLD. Sohn et al.[65] investigated the difference in hepatic fibrosis among subgroups of MAFLD and showed that the prevalence of significant fibrosis in lean/normal-weight MAFLD was similar to that in obese (BMI >25.0) MAFLD and was higher than that in overweight (BMI 23.0–24.9) MAFLD. Liu et al.[66] investigated the impact of MAFLD on liver-related events using a large-scale UK Biobank database (n=160,979). They reported that lean/normal weight MAFLD was associated with an increased risk of liver-related events independent of the five genetic variants (PNPLA3 rs738409 C/G, TM6SF2 rs58542926 C/T, GCKR rs1260326 T/C, MBOAT7 rs641738 C/T, and HSD17B13 rs72613567 T/TA).[66] Lin et al.[67] evaluated the impact of MAFLD on the recurrence of HBV-related HCC after curative resection and found that lean/normal weight MAFLD was a risk factor for tumor recurrence among patients with MAFLD (hazard ratio [HR], 2.030; 95% confidence interval [CI], 1.117–3.690; P=0.020) (Table 1). Fukunaga et al.[42] investigated the impact of MAFLD on the prevalence of colorectal adenoma in health check-up examinees. The authors demonstrated that lean/normal-weight MAFLD was the sole independent factor associated with the presence of colorectal adenoma (odds ratio [OR], 3.351; 95% CI, 1.589–7.262; P≤0.001). Lean/normal weight MAFLD was also the most important classifier for the presence of colorectal adenoma in data-mining analysis.[42] Semmler et al.[68] investigated the relevance of MAFLD for mortality and demonstrated that lean/normal-weight MAFLD had the worst survival rates. Although the number of studies in lean/normal-weight MAFLD is limited, this avalanche of publications in such a short time supports the validity of the lean/normal-weight MAFLD definition.

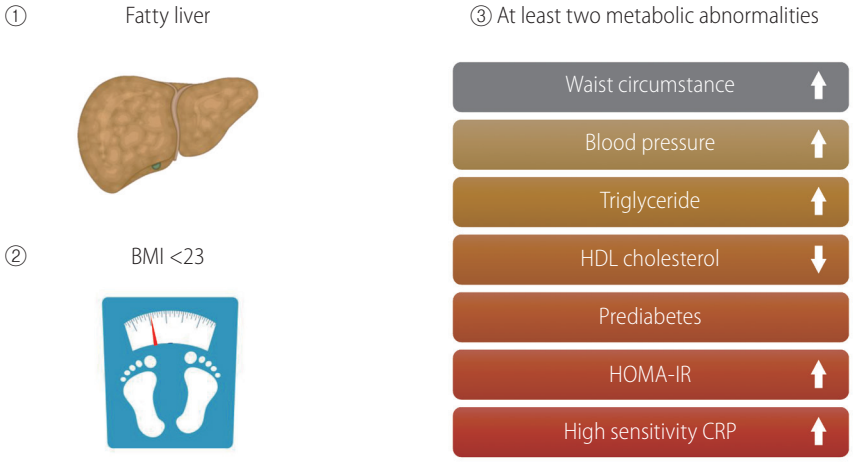

Figure 1. Definition of lean/normal weight MAFLD in the Asia-Pacific region. The definition requires ① the presence of fatty liver, ② BMI <23, and ③ at least two of the metabolic abnormalities. BMI, body mass index; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; CRP, C-reactive protein; MAFLD, metabolic dysfunction-associated fatty liver disease.

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Table 1. The interaction between MAFLD and HBV infection

Study	Number	Study design	Prevalence of MAFLD	Mean age (years)	Main outcome
Lin et al.[67] (2021)	812	Retrospective cohort study	45.4% of the patients with chronic hepatitis B-related hepatocellular carcinoma (296/1,076)	MAFLD: -56.2 Non-MAFLD: -56.2	Lean MAFLD (BMI <23 kg/m^2) was a relative risk factor for tumor recurrence (HR, 2.03) among patients with MAFLD
Mak et al.[73] (2020)	2,370	Retrospective cross-sectional study	45.7% of the patients with chronic hepatitis B (1,083/2,370)	MAFLD: -57.5 Non-MAFLD: -51.5	The patients with chronic hepatitis B plus MAFLD had a higher prevalence of severe steatosis compared to the patients with chronic hepatitis B plus NAFLD outside the MAFLD criteria (62.0% vs. 35.3%). The patients with chronic hepatitis B plus MAFLD had a higher prevalence of advanced fibrosis/cirrhosis compared to the patients with chronic hepatitis B plus NAFLD outside the MAFLD criteria (22.6% vs. 11.8%).
van Kleef et al.[74] (2021)	1,076	Retrospective cohort study	27.5% of the patients with chronic hepatitis B (296/1,076)	MAFLD: -43.6 Non-MAFLD: -36.7	MAFLD was independently associated with the poor event-free (adjusted HR, 2.00), hepatocellular carcinoma-free (adjusted HR, 1.93), and transplant-free (adjusted HR, 1.80) survival rates. Among the patients with MAFLD, no significant difference was seen in the event-free survival between the patients with and without steatohepatitis or between the patients with an NAFLD activity score <3 and those with an NAFLD activity score ≥3.
Wang et al.[75] (2021)	417	Retrospective cross-sectional study	All the subjects had MAFLD	MAFLD: -41.5	Among the patients with MAFLD, hepatitis B virus infection was associated with a significantly lower grade of hepatic steatosis (OR, 0.088), but higher levels of inflammation (OR, 4.059), and fibrosis (OR, 3.016) after adjusting for age, gender, and other metabolic parameters
Huang et al.[76] (2021)	185	Retrospective cross-sectional study	84.9% of the patients with biopsy-proven fatty liver or cryptogenic cirrhosis (157/185)	MAFLD-only: -51.9 NAFLD-only: -44.1	Advanced fibrosis was associated with the presence of hepatitis B virus infection and metabolic diseases

MAFLD, metabolic dysfunction-associated fatty liver disease; HBV, hepatitis B virus; BMI, body mass index; HR, hazard ratio; OR, odds ratio.

IMPORTANCE OF MULTIPLE ETIOLOGIES OF LIVER DISEASE: MAFLD, VIRAL HEPATITIS, AND ALCOHOLIC INTAKE

HBV and HCV infection rates are high in the Asia-Pacific region. In patients with viral hepatitis, fatty liver is observed in 30% to 40%,[26,27] and co-existing fatty liver has been reported to be associated with a higher risk of HCC in patients with HBV infection.[69] The presence of fatty liver has also been reported to increase the risk of HCC even in patients with HCV infection who achieve a cure with DAA therapy.[70] In addition, alcoholic liver disease is a common cause of chronic liver disease in the Asia-Pacific region.[71] Co-existing alcoholic liver disease and hyperalimentation-associated fatty liver shows synergistic interaction, resulting in the progression of liver disease.[72] These findings imply that assessment of fatty liver is important for the clinical management of patients with viral hepatitis and alcohol intake, especially in the Asia-Pacific region (Fig. 2).

A unique feature of the MAFLD definition is that a diagnosis of MAFLD can be made irrespective of the diagnosis of any other liver disease, including viral hepatitis. This allows clinicians to investigate the interaction between viral hepatitis and MAFLD. Mak et

al.[73] investigated the impact of MAFLD in patients with HBV infection (Table 1). They found that 45.7% of patients (1,083/2,370) fulfilled the criteria of both CH-B and MAFLD. Patients with CH-B plus MAFLD had a higher prevalence of advanced fibrosis/cirrhosis compared to patients with CH-B alone (22.6% vs. 11.8%).[73] Likewise, van Kleef et al.[74] investigated the impact of MAFLD on adverse clinical outcomes in patients with HBV infection (Table 1). MAFLD was independently associated with poor event-free (adjusted HR, 2.00; 95% CI, 1.26–3.19), HCC-free (adjusted HR, 1.93; 95% CI, 1.17–3.21), and transplant-free (adjusted HR, 1.80; 95% CI, 0.98–3.29) survival rates.[74] In other studies, Wang et al.[75] demonstrated that HBV infections were associated with a significantly lower grade of hepatic steatosis in patients with MAFLD (OR, -0.088; 95% CI, -0.027 to 0.291), but higher inflammation (OR, -4.059; 95% CI, -1.403 to 11.742), and fibrosis (OR, -3.016; 95% CI, -1.087 to 8.370) rates after adjusting for age, gender, and other metabolic parameters. Huang et al.[76] also showed that advanced hepatic fibrosis was associated with the presence of both HBV infections and metabolic disease. Therefore, there is a clinically meaningful interaction between MAFLD and HBV infection.

Similar data are available for patients with HCV infection. In patients with HCV infection, DAAs are currently the standard of care and achieve high cure rates in real-world settings.[10] Treatment with DAAs reduces liver stiffness; however, this is negatively associated with an increase in the severity of fatty liver.[77,78] Co-existing fatty liver is also a risk factor for HCC after cure in patients with HCV infection.[79,80] Furthermore, Peleg et al.[81] demonstrated that fatty liver is a major predictor of all-cause mortality in patients who achieve a sustained virological response following DAA treatment, regardless of fibrosis stage. Thus, MAFLD should be treated and managed on its own merits, even in patients with cured HCV infection. Fouad et al.[82] proposed the importance of a holistic and multidisciplinary approach for the management of the growing number of patients with treated HCV who achieved cure, since the global prevalence of previous/current infection is likely well in excess of 150 million. To date, no study employed MAFLD to examine the impact of fatty liver with metabolic dysfunction on clinical outcomes in patients with HCV infection after cure. However, previous studies have indicated that MAFLD is useful for assessing the morbidity and mortality of patients with HCV infection who have achieved this endpoint.

Alcoholic liver disease is also a common cause of liver disease in the Asia-Pacific region.[71] In this population, heterozygosity for the aldehyde dehydrogenase 2×2 allele, which results in lower enzymatic activity, is highly prevalent, with the incidence reaching 45% in East Asia.[71,83] Whereas, in India, 96.3% of patients with alcoholic liver disease have at least one component of metabolic syndrome and 53.0% has three or more components of metabolic syndrome, suggesting the high prevalence of co-existence of alcoholic liver disease and hyperalimentation-associated fatty liver.[84,85] Patients with both alcoholic and NAFLD have higher serum levels of aminotransferases and a high prevalence of advanced fibrosis than in patients with NAFLD.[86] Harmful effect of mild-to-moderate alcohol intake on hepatic fibrosis was seen in patients with metabolic syndrome, but not in patients with no metabolic syn-

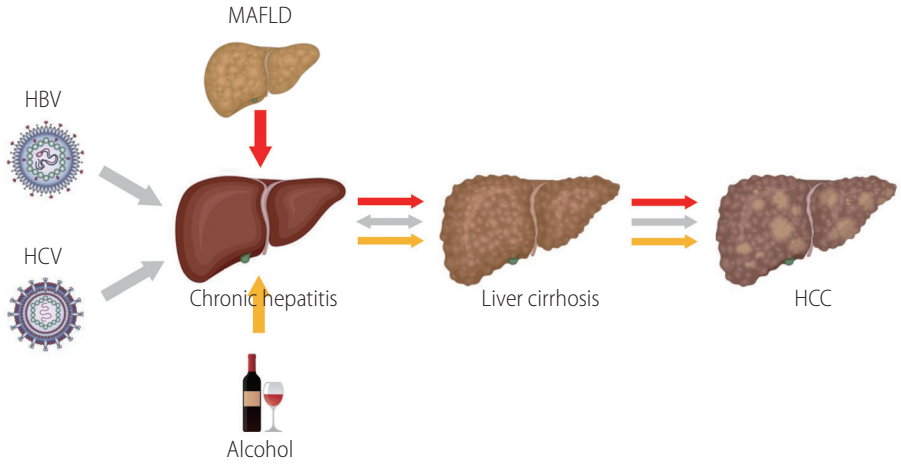

Figure 2. MAFLD accelerates the progression of liver disease in patients with HBV/HCV infection. Co-existing MAFLD is a higher risk for liver cirrhosis and HCC in patients with HBV and HCV infection. HBV, hepatitis B virus; HCV, hepatitis C virus; MAFLD, metabolic dysfunction-associated fatty liver disease; HCC, hepatocellular carcinoma.

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drome.[87] In patients with MAFLD, even modest alcohol intake has been reported to be associated with significant hepatic fibrosis in Asia.[40] Thus, previous studies suggest that alcohol intake exacerbates the progression of liver disease in patients with MAFLD. Future research may be focused on the effects of MAFLD on life-threatening events and prognosis in patients with alcoholic liver disease, and vice versa.

MAFLD-RELATED HCC: A PROPOSED NEW CLASSIFICATION FOR THE ETIOLOGY OF HCC

Fatty liver causes lipotoxicity and oxidative stress in the liver; both are well-established drivers of hepatocarcinogenesis, while hepatic steatosis is recognized as an independent risk factor.[88-92] Fatty liver has been frequently categorized in the Asia-Pacific region as non-B non-C or non-viral HCC, probably because fatty liver represents a minor etiological cause of HCC in the region.[28-31] Non-B non-C HCC includes not only fatty liver but also other liver diseases, such as alcoholic liver disease, autoimmune liver diseases, and genetic liver diseases. Moreover, non-B non-C HCC is separate from HBV/HCV-related HCC, and co-existing fatty liver is not considered in the current etiological classification of HCC (Fig. 3).

Non-B non-C HCC is now becoming the leading cause of HCC in many countries of the Asia-Pacific region following the control and treatment of viral hepatitis.[30,53,93-96] Eighty-five percent of patients with non-B non-C HCC have at least one risk factor for MAFLD, suggesting that it is the dominant etiology for non-B non-C HCC.[97] The prevalence of fatty liver-related HCC is estimated to increase by 47% in Japan and 86% in China by 2030.[98] In addition, HCC often occurs in patients with fatty liver who do not have cirrhosis[99,100] and tends to be diagnosed at an advanced stage.[28,101] Therefore, these patients require a different screening strategy.

No cohort studies have demonstrated that MAFLD is associated with a higher HCC risk. Furthermore, it remains unclear whether MAFLD-related HCC cells have specific pathological features including a steatohepatitic phenotype. In addition, there is insufficient evidence to modify the treatment of HCC patients according to the HCC etiology. However, accumulated evidence demonstrates that obesity, type 2 diabetes, and metabolic syndrome are risk factors for HCC in patients with fatty liver, all embodied in the MAFLD definition.[19-22,102-106] Moreover, co-existing fatty liver is a risk factor for HCC in patients with HBV/HCV infection.[69,70,79,107,108] Recently, Pfister et al.[109] performed a meta-analysis and demonstrated that non-viral HCC is less responsive to immunotherapy. Non-viral HCC does not equal MAFLD-related HCC. However, there was an increase in the number of $CD8^+PD1^+$T cells in the liver of a NASH-related HCC mouse model.[109] Additionally, the $CD8^+PD1^+$T cells showed high thymocyte selection-associated high mobility group box protein expression levels,[109] which reduced the degradation of PD-1 and promoted its translocation to

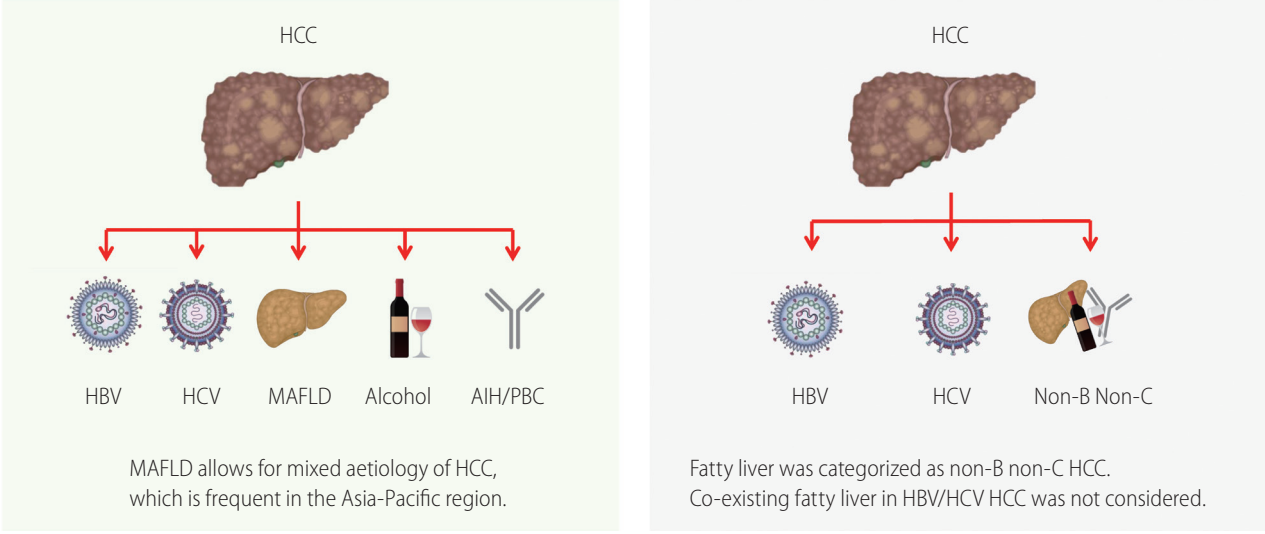

Figure 3. MAFLD renovates the etiological classification of HCC. The clinical features of HCC differ depending on its etiology. MAFLD should be categorized as an independent single etiology for HCC rather than mixing up as non-B non-C. MAFLD also allows for mixed etiology of HCC, which is frequent in the Asia-Pacific region. HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; MAFLD, metabolic dysfunction-associated fatty liver disease; AIH, autoimmune hepatitis; PBC, primary biliary cholangitis.

the surface of the T cells, leading to an impairment of the immune surveillance.[109,110] Therefore, the efficacy of immunotherapy for MAFLD-related HCC may be limited compared to the other HCC etiologies. Although robust evidence is lacking, MAFLD could be categorized as an independent etiological cause of HCC, especially in the immunotherapy era (Fig. 3). This new classification will promote the development of novel context-specific strategies for the prevention and treatment of HCC in the Asia-Pacific region.

SARCOPENIA AND A LOW-INTENSITY EXERCISE PROGRAM FOR MAFLD

Physical inactivity causes loss of skeletal muscle, a major organ that determines resting energy expenditure.[111,112] In patients with MAFLD, Chun et al.[113] investigated the impact of sarcopenia on hepatic fibrosis and ASCVD risk using a large, population-based cohort. They found that sarcopenia was associated with significant hepatic fibrosis and risk of ASCVD in patients with MAFLD. Whereas, O'Gorman et al.[114] performed a non-randomized controlled trial and found that 12 weeks of moderate-to-vigorous intensity aerobic exercise reduced fibrosis and hepatocyte ballooning by one stage in 58% and 67% of patients, respectively, in the absence of clinically significant weight loss. Thus, exercise is an important treatment for patients with MAFLD.

A reduction in physical activity is seen in approximately 50% of patients with fatty liver in Asia.[115] In addition, patients with MAFLD are at high risk for ASCVD. Therefore, moderate-to-vigorous intensity exercise may be impracticable in many patients. Recently, a low-intensity resistance exercise program was developed based on the results of a meta-analysis of exercise for patients with fatty liver (Fig. 4).[116] This low-intensity resistance exercise program was feasible even for subjects with no exercise habits. The program altered the expression of microRNA (miR)-630, miR-5703, and fractalkine, which are associated with the inhibition of cancer cell proliferation.[117-119] Therefore, even low-intensity exercise may exert beneficial effects through alterations in miR and fractalkine expression in humans. A practicable exercise program is an unmet medical need for patients with MAFLD in the Asia-Pacific region. Future research should be focused on better low-intensity exercise for patients with MAFLD.

MAFLD IMPROVES DISEASE AWARENESS

NAFLD is diagnosed based on the amount of alcohol intake and the exclusion of other causes of hepatic steatosis. In these patients, lifestyle intervention is one of the cornerstones of current management.[12,120,121] However, the effect of mild-to-moderate alcohol intake differs based on individual characteristics, including body weight, sex, and genetic polymorphisms in enzymes of alcohol metabolism.[122-124] In addition, patient understanding is the first

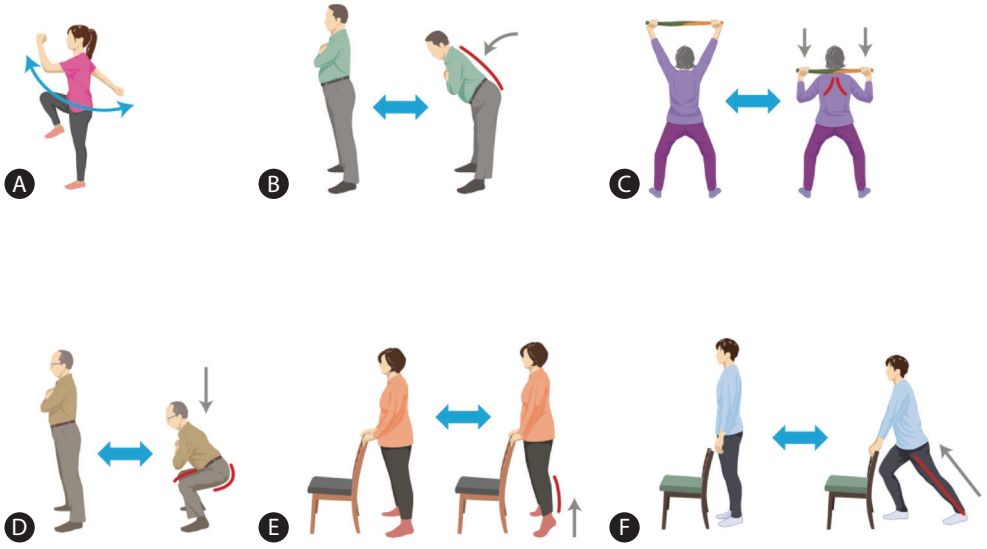

Figure 4. Scheme for a low-intensity resistance exercise program based on a meta-analysis. The exercise consists of six types of exercises such as (A) stepping, (B) good-morning exercises, (C) towel lat pulldowns, (D) squats, (E) calf raises, and (F) triceps surae stretching. The figure is adopted from an article by Hashida et al.[116] with permission from John Wiley and Sons.

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step toward improving their lifestyle, and most patients are unable to understand the meaning of "non-alcoholic."[34] Similarly, most non-specialist physicians lack awareness of the importance of fatty liver[35] and are unfamiliar with the difference between NAFLD and non-alcoholic steatohepatitis.[125] Furthermore, Muslims are widely distributed in the Asia-Pacific region, in particular West Asia. Islam prohibits alcohol consumption, and there is still a stigma associated with the term "non-alcoholic."[126]

MAFLD is independent of alcohol intake and clearly indicates the etiology of fatty liver to be "metabolic dysfunction." Fouad et al.[35] recently performed a survey in Egypt showing that 73.3% of physicians reported that they became more familiar with fatty liver disease after the name changed from NAFLD to MAFLD. Moreover, Méndez-Sánchez et al.[127] from Mexico reported that 65.7% of participants became more familiar with fatty liver disease following the redefinition to MAFLD. Furthermore, MAFLD has had a positive impact on nurses and allied health personnel's ability to motivate patients to undertake lifestyle changes.[128] In addition, an international expert panel recently proposed a definition of MAFLD for children.[129] Accordingly, MAFLD may help improve disease awareness of patients, doctors, medical staff, and various stakeholders. This improvement will contribute to the development of prevention and treatment strategies, including pharmacotherapies, resulting in an improvement in patient-reported outcomes and a reduction in healthcare costs.[130] Several associations and expert panels have published consensus/position statements to endorse "MAFLD" as the official term.[126,131-134]

ISSUES TO BE RESOLVED

One of the issues with the MAFLD definition is the exclusion of fatty livers in the absence of metabolic dysfunction. Therefore, future studies should focus on the impact of the new criteria on intra- and extra-hepatic outcomes and prognoses by comparing the NAFLD criteria. Caution should also be used when managing patients who have fatty livers but not metabolic dysfunction, as they may be consuming alcohol surreptitiously, they may have an undiscovered cause of the excess liver fat or another disease that has not been tested for (e.g., lysosomal acid lipase deficiency), or they may develop MAFLD over time. Additionally, there is no requirement to exclude other contributing liver disease etiologies when diagnosing a patient with MAFLD. In clinical practice, however, it is important to test for other diseases, as they may exist concomitantly with MAFLD and thus should be managed appropriately.

CONCLUSION

In this review, we described the distinctive characteristics of fatty liver in the Asia-Pacific region. We also summarized the many advantages of using the definition of MAFLD in this regional context (Fig. 5). Although studies using the MAFLD criteria are in their infancy, a more precise definition of MAFLD in lean/normal-weight people will help standardize and promote the clinical and translational investigation of this unique phenotype. The concept

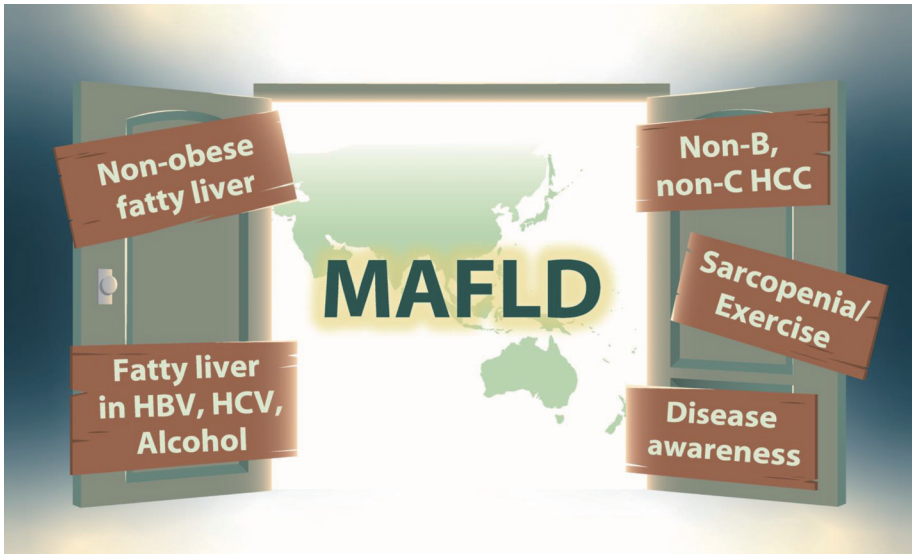

Figure 5. Scheme for MAFLD enhances clinical practice for liver disease in the Asia-Pacific region. HBV, hepatitis B virus; HCV, hepatitis C virus; MAFLD, metabolic dysfunction-associated fatty liver disease; HCC, hepatocellular carcinoma.

of MAFLD is also particularly useful to disentangle the impact of concomitant fatty liver in patients with viral hepatitis, which is prevalent in the Asia-Pacific region. MAFLD will likewise reconstruct the etiological classification of and therapeutic strategies for HCC. The term MAFLD highlights the impact of metabolic dysfunction on pathogenesis and the importance of lifestyle interventions, including exercise. Last but not least, the term "MAFLD" itself may increase disease awareness, leading to improvements in natural history and clinical outcomes, patient-reported outcomes, and the economic burden to patients and national healthcare systems.

Authors' contribution

All authors were responsible for drafting and critical revision of the manuscript for important intellectual content.

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Conflicts of Interest

Takumi Kawaguchi received lecture fees from Janssen Pharmaceutical K.K., Mitsubishi Tanabe Pharma Corporation, and Otsuka Pharmaceutical Co., Ltd. The other authors have no conflicts of interest.

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