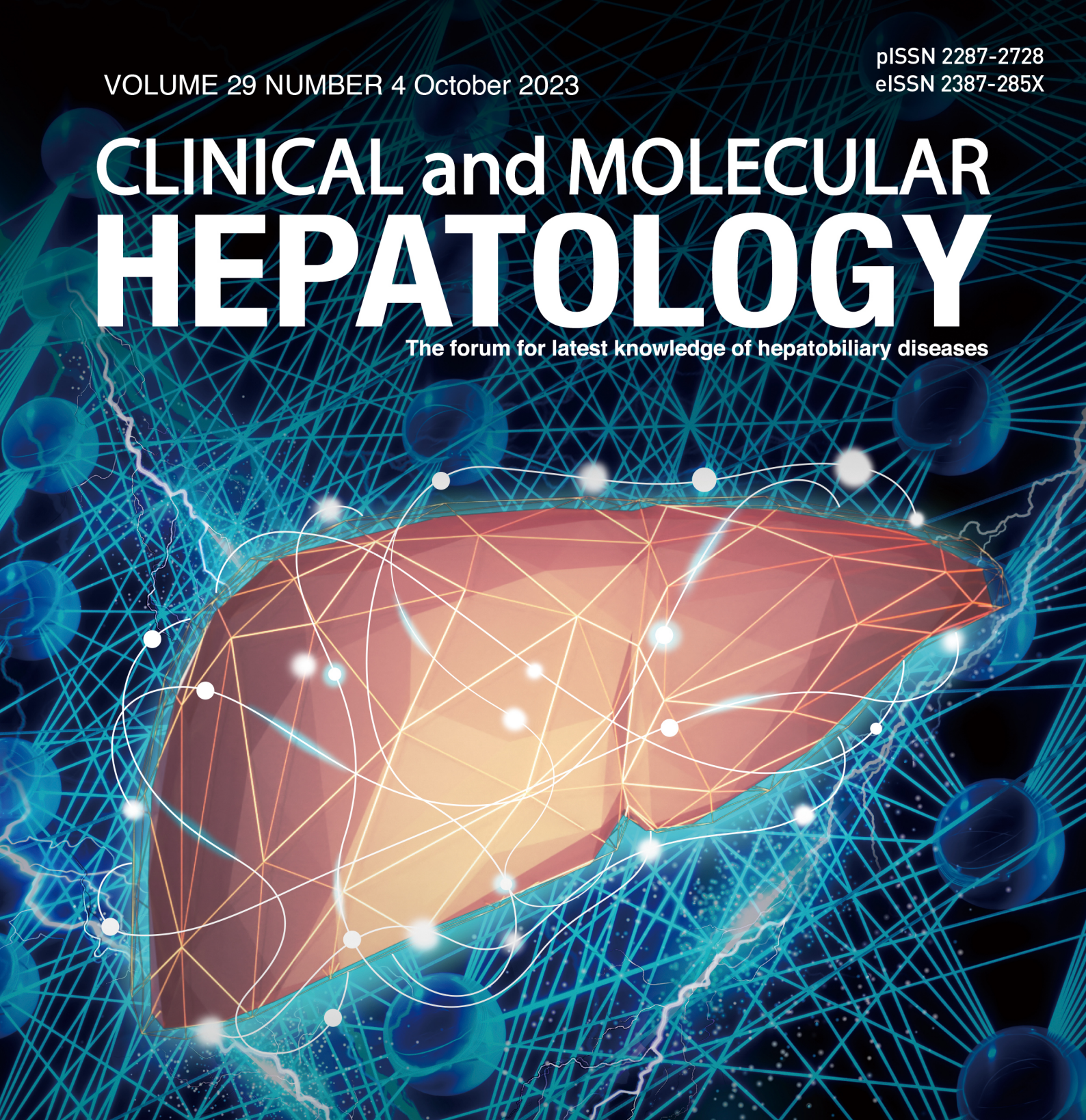
VOLUME 29 NUMBER 4 October 2023
pISSN 2287-2728
eISSN 2387-285X

CLINICAL and MOLECULAR HEPATOLOGY

The forum for latest knowledge of hepatobiliary diseases



Deep learning-based CT analysis in CHB patients

Lean NAFLD & mortality
Ranking of locoregional treatments for small HCC
Visceral fat obesity, sarcopenia, myosteatosis in NAFLD without obesity

KASL

pISSN 2287-2728
eISSN 2287-285X

CLINICAL and MOLECULAR HEPATOLOGY

https://doi.org/10.3350/cmh.2023.0359
Clinical and Molecular Hepatology 2023;29:969-972

Editorial

From nonalcoholic steatohepatitis, metabolic dysfunction-associated fatty liver disease, to steatotic liver disease: Updates of nomenclature and impact on clinical trials

Ming-Lun Yeh[1,2] and Ming-Lung Yu[1,2,3]

[1]School of Medicine, College of Medicine, Kaohsiung Medical University; [2]Hepatobiliary Division, Department of Internal Medicine, Kaohsiung Medical University Hospital; [3]School of Medicine, College of Medicine and Center of Excellence for Metabolic Associated Fatty Liver Disease, National Sun Yat-sen University, Kaohsiung, Taiwan

Keywords: NAFLD; MAFLD; SLD; MASLD; Steatosis

See Article on Page 831

With a growing prevalence, nonalcoholic fatty liver disease (NAFLD) has become the primary etiology of liver disease worldwide.[1,2] However, the exclusionary diagnostic criteria raise concerns about using the term "NAFLD." In 2020, a panel of international experts from 22 countries proposed a new nomenclature of "metabolic dysfunction-associated fatty liver disease (MAFLD)" by a panel of experts in this field.[3] As the name suggests, MAFLD emphasizes the importance of metabolic dysfunction that can be observed from the new definitions of overweight/obesity, type 2 diabetes, or at least two metabolic risk abnormalities, irrespective the etiologies and comorbidities, such as alcoholism and viral hepatitis. However, ignoring alcoholism and other specific etiologies raises concerns about the contributions of hepatic steatosis in the progression of liver disease and the stigmatization of the term "fatty". Recently, a new nomenclature, "Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD)," was set up by three pan-national liver associations to replace "NAFLD" and "MAFLD".[4,5]

In the current issue of *Clinical and Molecular Hepatology*, Kim et al.[6] present their views regarding the potential impact of the new nomenclature "MASLD" on screening, diagnosis, treatment, and future drug development. Perspectives from hepatologists and endocrinologists were included as well. Unlike the negative criterion of NAFLD, MAFLD used a positive criterion and focused more on the linkage of metabolic abnormalities that were seen by the diagnostic criteria. More patients are diagnosed without the exclusion of other specific etiologies, and the disease awareness of physicians and patients has also improved. The most common cause of mortality in NAFLD patients was cardiovascular disease, followed by extrahepatic cancers.[7] It was reported that MAFLD patients had a greater risk for all-cause mortality compared to

Corresponding author : Ming-Lung Yu
Hepatobiliary Division, Department of Internal Medicine, Kaohsiung Medical University Hospital, 100 Tzyou Road, Kaohsiung City 807, Taiwan
Tel: +886-7-312-1101 ext. 7475, Fax: +886-7-312-3955, E-mail: fish6069@gmail.com
https://orcid.org/0000-0001-8145-1900

Editor: Seung Up Kim, Yonsei University College of Medicine, Korea

Received : Sep. 15, 2023 / **Accepted :** Sep. 18, 2023

NAFLD patients.[8] Other reports also demonstrated an increased cardiovascular mortality of patients with MAFLD as compared to NAFLD.[9] Similar results were also found in the risk of all types of cancers.[10] That means the transition from NAFLD to MAFLD helps identify more subjects who are at risk of extrahepatic events, and further promotes the surveillance of extrahepatic diseases in clinical practice. Moreover, MAFLD also provides the opportunity to evaluate the interaction between NAFLD and hepatitis B virus (HBV) and hepatitis C virus (HCV).[11]

However, as mentioned in this review, the abandonment of "steatohepatitis" disturbs the evaluation of hepatic severity and development of pharmaceutical agents. Meanwhile, the complete ignoring of alcohol consumption in MAFLD may confuse clinical judgment regarding the contributions of alcohol in hepatic progression. It is the same with the other specific etiologies that will also lead to hepatic steatosis and disease progression.

Different from NAFLD and MAFLD, the new term "Steatotic liver disease (SLD)" separates patients with or without cardiometabolic risk factors (CMRFs) and further classifies patients with CMRFs as "MASLD," which indicates no specific etiology of steatosis, and "MetALD or other combined etiology" for those with a moderate amount of alcohol consumption or drug or monogenic disease-related steatosis. Those without CMRFs are categorized as "alcohol-related liver disease (ALD)" or "specific etiology SLD," like drug-induced, monogenic, and miscellaneous, and "cryptogenic SLD" that not belong to the above categories. The new nomenclature "MASLD" also considers the hepatic progression form with a new term, "metabolic associated steatohepatitis (MASH)," which can be used as future guidance in clinical trials. The definition of alcohol amount is one of the points that differentiates SLD from NAFLD and MAFLD. Unlike the strict threshold of alcohol amounts in NAFLD and no threshold in MAFLD. A new category, "MetALD" is set up for those who consume moderate amounts of alcohol. The alcohol criteria of MetALD were made based on the general agreement that 30–60 gm of daily alcohol consumption would affect the natural history of NAFLD and possibly alter the response to therapeutic interventions. Recently, data from UK Biobank demonstrated that the MetALD group comprised predominantly males, and diabetes mellitus was significantly more prevalent in the MASLD group.[12] The MetALD group also exhibited higher levels of liver enzymes but lower levels of high-density lipoprotein (HDL) cholesterol. The data implied the potential role of dyslipidemia in the pathogenesis and differentiation of MetALD and MASLD.

From the perspectives of hepatologists, both of the two new terminologies can increase disease awareness among patients and physicians.[13] They are also expected to affect clinical practice positively, including the diagnostic process, non-pharmacologic approach, and potential treatment candidates. For clinical outcomes, the new subtypes of SLD might help identify more subjects at risk, either hepatic or extrahepatic. The new terminology operates subjects based on the amount of alcohol consumption that enables the development of proper treatment strategies accordingly and further helps to understand the influences of alcohol consumption in disease progression. Nevertheless, the criteria of alcohol consumption remain based on expert opinion and agreement, without scientific evidence. It is also difficult to assess alcohol consumption precisely in clinical practice.

The FDA recommends endpoints of clinical trials for accelerated approval of nonalcoholic steatohepatitis (NASH), including either improvement in steatohepatitis or fibrosis. Therefore, MAFLD is usually not included in the clinical trial enrollment criteria due to the lack of the term "steatohepatitis." The new MASLD, with the progression form MASH, is expected to allow clinical trial enrollment. However, MASH also excludes NASH patients without CMRF from NASH treatment, although it might be rare. Whether the potential therapeutic agents for NASH could be generalized to MASH patients needs further investigation.

Despite that, several challenging issues of SLD remain.

1) There is difficulty in developing disease-specific biomarkers or agents for patients with MASLD, MetALD, and ALD. The dynamic changes in metabolic health and alcohol

Abbreviations:

NAFLD, nonalcoholic fatty liver disease; MAFLD, metabolic dysfunction-associated fatty liver disease; MASLD, metabolic dysfunction associated steatotic liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus; SLD, steatotic liver disease; CMRFs, cardiometabolic risk factors; ALD, alcohol-related liver disease; MASH, metabolic associated steatohepatitis; HDL, high density lipoprotein; SGLT2, glucose-lowering agents, sodium-glucose cotransporter 2; GLP1, glucagon-like peptide 1; NASH, nonalcoholic steatohepatitis

https://doi.org/10.3350/cmh.2023.0359

consumption over time also raise the concern of making the diagnosis at a specific time. Currently, subjects who consume high amounts of alcohol together with metabolic dysfunction (positive CMRFs) are classified as ALD. However, this group of patients may have different disease pathogenesis, course, and outcomes than those without metabolic dysfunction.

2) Patients with HCV infection are classified as "miscellaneous SLD." At least 20% of subjects have a spontaneous resolution from acute HCV infection, and most of the chronically infected patients are now eradicated owing to the current high-efficacy antiviral drugs.[14] Chronic HCV infections are associated with the risks of extrahepatic manifestations, which frequently correlate to fatty liver, DM, cardiovascular comorbidities,[15] even after HCV eradication.[16,17] The role of metabolic dysfunction in the development of SLD before and after HCV eradication is clinically important, and it should not be excluded from clinical practice for SLD. Whether classifying it as HCV-SLD or HCV-MASLD may need further exploration.

3) HBV infection remains highly prevalent in middle- to old-aged Asians. However, HBV infection is not included in the new terminology regarding whether a specific classification of HBV should be made or not. Accumulating data have suggested that fatty liver and obesity facilitated higher chance of HBV surface antigen clearance and lower risk of cirrhosis and HCC in the natural course[18] and during antiviral therapy.[19] In contrast, coincidence of fatty liver and metabolic dysfunction increased the risk of hepatocellular carcinoma.[20] Again, the interplay between HBV and SLD/MASLD should not be ignored in clinical practice.

From the perspectives of endocrinologists, the cardiometabolic risk threshold to determine metabolic dysfunction in SLD is discussed. As mentioned, using only one CMRF as the criteria may cause over-estimation of MASLD/MetALD and under-estimation of other types of SLD. Meanwhile, young and lean subjects with hepatic steatosis without any metabolic risk factors will be classified as cryptogenic SLD, even if they may share the same disease pathophysiology. Concerning the treatment of MASLD, therapeutic agents that are effective in metabolic syndrome may reverse MASLD. Same as for NAFLD/MAFLD, lifestyle modifications are the cornerstone, but are challenging for most patients. The glucose-lowering agents, sodium-glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide 1 (GLP 1) receptor agonists, have been shown to improve steatohepatitis and reduce cardiovascular risk. Thus, they may be applied in the treatment of MASLD, especially in those with type 2 diabetes. In the last part, the interaction between insulin resistance and alcohol consumption is discussed. However, the safe alcohol amount due to individual genetic differences and the relative contributions of metabolic dysfunction and alcohol to MetALD disease progression remain uncertain.

To conclude, Kim et al.[6] reviewed the new terminology of SLD and its subclassifications, as well as the advantages and insufficiencies of the new terminology. As mentioned, future research is recommended for the new biomarkers and drugs for MASLD. Further explorations regarding the natural course and disease prognosis of the subtypes of SLD, especially MASLD, MetALD, and concomitant of viral hepatitis, are also necessary.

Authors' contribution

ML Yeh drafted the manuscript. ML Yu reviewed and finalized the manuscript.

Conflicts of Interest

The authors have no conflicts to disclose.

REFERENCES

1. Younossi ZM, Golabi P, Paik JM, Henry A, Van Dongen C, Henry L. The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): a systematic review. Hepatology 2023;77:1335-1347.
2. Alqahtani SA, Chan WK, Yu ML. Hepatic outcomes of nonalcoholic fatty liver disease including cirrhosis and hepatocellular carcinoma. Clin Liver Dis 2023;27:211-223.
3. Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, et al. A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. J Hepatol 2020;73:202-209.
4. Rinella ME, Lazarus JV, Ratziu V, Francque SM, Sanyal AJ, Kanwal F, et al. A multi-society Delphi consensus statement on new fatty liver disease nomenclature. Hepatology 2023 Jun 24. doi: 10.1097/HEP.0000000000000520.
5. Rinella ME, Lazarus JV, Ratziu V, Francque SM, Sanyal AJ, Kanwal F, et al. A multi-society Delphi consensus statement on new fatty liver disease nomenclature. J Hepatol 2023 Jun 20. doi: 10.1016/j.jhep.2023.06.003.

6. Kim GA, Moon JH, Kim W. Critical appraisal of metabolic dysfunction-associated steatotic liver disease: Implication of Janus-faced modernity. Clin Mol Hepatol 2023 Aug 25. doi: 10.3350/cmh.2023.0277.
7. Konyn P, Ahmed A, Kim D. Causes and risk profiles of mortality among individuals with nonalcoholic fatty liver disease. Clin Mol Hepatol 2023;29(Suppl):S43-S57.
8. Huang Q, Zou X, Wen X, Zhou X, Ji L. NAFLD or MAFLD: Which has closer association with all-cause and cause-specific mortality?-results from NHANES III. Front Med (Lausanne) 2021;8:693507.
9. Gofton C, Upendran Y, Zheng MH, George J. MAFLD: How is it different from NAFLD? Clin Mol Hepatol 2023;29(Suppl):S17-S31.
10. Wei S, Hao Y, Dong X, Huang J, Huang K, Xie Y, et al. The relationship between metabolic dysfunction-associated fatty liver disease and the incidence rate of extrahepatic cancer. Front Endocrinol (Lausanne) 2023;14:985858.
11. Huang JF, Tsai PC, Yeh ML, Huang CF, Huang CI, Lee MH, et al. Community-centered disease severity assessment of metabolic dysfunction-associated fatty liver disease. J Clin Transl Hepatol 2023;11:1061-1068.
12. Schneider KM, Schneider CV. A new era for steatotic liver Disease: Evaluating the Novel nomenclature in the UK Biobank. J Hepatol 2023 Jul 13. doi: 10.1016/j.jhep.2023.07.007.
13. Younossi ZM, Ong JP, Takahashi H, Yilmaz Y, Eguc Hi Y, El Kassas M, et al. A global survey of physicians knowledge about nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2022;20:e1456-e1468.
14. Yu ML, Chuang WL. Path from the discovery to the elimination of hepatitis C virus: Honoring the winners of the Nobel Prize in Physiology or Medicine 2020. Kaohsiung J Med Sci 2021;37:7-11.
15. Younossi ZM, Henry L, P Ong J, Tanaka A, Eguchi Y, Mizokami M, et al. Systematic review with meta-analysis: extrahepatic manifestations in chronic hepatitis C virus-infected patients in East Asia. Aliment Pharmacol Ther 2019;49:644-653.
16. Jang TY, Lin YH, Liang PC, Yeh ML, Huang CI, Liu TW, et al. Amelioration of glucose intolerance through directly acting antiviral agents in chronic hepatitis C cirrhotic patients without overt diabetes. Kaohsiung J Med Sci 2022;38:897-906.
17. Huang CF, Dai CY, Yeh ML, Huang CI, Lee HC, Lai WT, et al. Cure or curd: Modification of lipid profiles and cardio-cerebrovascular events after hepatitis C virus eradication. Kaohsiung J Med Sci 2020;36:920-928.
18. Wong YJ, Nguyen VH, Yang HI, Li J, Le MH, Wu WJ, et al. Impact of fatty liver on long-term outcomes in chronic hepatitis B: a systematic review and matched analysis of individual patient data meta-analysis. Clin Mol Hepatol 2023;29:705-720.
19. Li J, Yang HI, Yeh ML, Le MH, Le AK, Yeo YH, et al. Association between fatty liver and cirrhosis, hepatocellular carcinoma, and hepatitis B surface antigen seroclearance in chronic hepatitis B. J Infect Dis 2021;224:294-302.
20. Huang SC, Su TH, Tseng TC, Chen CL, Hsu SJ, Liao SH, et al. Distinct effects of hepatic steatosis and metabolic dysfunction on the risk of hepatocellular carcinoma in chronic hepatitis B. Hepatol Int 2023 May 29. doi: 10.1007/s12072-023-10545-6.