Rethinking Metabolic Dysfunction in Chronic Liver Diseases

Lung-Yi Loey Mak[1,2]

1. Department of Medicine, School of Clinical Medicine, The Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China; 2. State Key Laboratory of Liver Research, The Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China

https://doi.org/10.17925/EE.2026.22.1.5

Metabolic dysfunction is a concept derived from metabolic syndrome, which is characterized by the presence of metabolic abnormalities, including obesity, diabetes mellitus, hypertension and dyslipidaemia. Metabolic dysfunction not only drives the development of metabolic dysfunction-associated steatotic liver disease but is also responsible for the heightened cardiovascular risk within the broader scope of liver–cardiovascular–kidney–metabolic syndrome. In other chronic liver diseases, metabolic dysfunction alters the natural history and might impact treatment outcomes.

Keywords

Cardiovascular disease, cardiovascular–kidney–metabolic (CKM) syndrome, cirrhosis, hepatocellular carcinoma, metabolic syndrome, mortality

Disclosures: Lung-Yi Loey Mak received research grant funding from Gilead Sciences and Roche Diagnostics.

Acknowledgements: No AI or LLM tools were used in the creation or processing of this article.

Review process: Double-blind peer review.

Compliance with ethics: This article is an opinion piece and does not report on new clinical data, or any studies with human or animal subjects performed by the author.

Data availability: Data sharing is not applicable to this article as no datasets were generated or analysed during the writing of this article.

Authorship: The named author meets the criteria of the International Committee of Medical Journal Editors for authorship for this manuscript, takes responsibility for the integrity of the work as a whole and has given final approval for the version to be published.

Access: This article is freely accessible at touchENDOCRINOLOGY.com. © Touch Medical Media 2026.

Received: 27 November 2025

Accepted: 30 January 2026

Published online: 2 March 2026

Citation: *touchREVIEWS in Endocrinology.* 2026;22(1):Online ahead of journal publication

Corresponding author: Lung-Yi Loey Mak, Room 306, Professorial Block, Pokfulam Road 102, Queen Mary Hospital, Hong Kong, China. E: lungyi@hku.hk

Support: No funding was received in the publication of this article.

The global prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) has increased over the past three decades and is estimated to be 30% as of 2022.[1] As an indication of disease burden, MASLD-related liver transplantation has already surpassed many other aetiologies as a leading indication of transplant waitlisting in the West.[2] Metabolic dysfunction underlies the pathogenesis of MASLD and is defined when at least one of the five cardiometabolic conditions, encompassing overweight/obesity, prediabetes/diabetes, hypertension, hypertriglyceridaemia and low high-density lipoprotein cholesterol, is present, which leads to lipid accumulation in the liver, steatohepatitis, cirrhosis and liver cancer.[3] The concept of metabolic dysfunction emerged from the more well-known and established metabolic syndrome, which requires at least three out of five criteria for diagnosis.[4] Incorporating metabolic dysfunction into the diagnostic criteria for MASLD aids the identification of patients who have high-risk phenotypes, including significant liver fibrosis and abnormal liver enzymes, as well as high-risk groups for developing adverse hepatic outcomes. This contrasts with the old criteria, 'non-alcoholic fatty liver disease (NAFLD)', which is basically a diagnosis by exclusion. Among the disease-defining conditions, type 2 diabetes (T2D) is associated with the highest risk of disease progression in MASLD. In a study of 2,016 participants with MASLD, T2D was associated with a significantly increased risk of hepatic decompensation and hepatocellular carcinoma compared with participants without T2D.[5] A higher number of cardiometabolic criteria was found to be associated with a higher cumulative incidence of major adverse cardiovascular events, but not liver-related events.[6] To quantify the severity of metabolic dysfunction, apart from measuring the homeostatic model assessment for insulin resistance, circulating sulphatides – a type of sulphated glycosphingolipids – and highly sensitive C-reactive protein have been shown to correlate with liver fibrosis severity in MASLD.[7,8] Therefore, metabolic dysfunction is not just a defining feature of MASLD but also contributes to disease prognostication and outcome prediction. MASLD should be actively sought among patients with evidence of metabolic dysfunction frequently encountered in endocrinology or primary care settings, starting with imaging to confirm the presence of hepatic steatosis, followed by non-invasive tests (such as Fibrosis-4 Index [FIB-4] or vibration-controlled transient elastography) to stratify the risk of liver fibrosis.

Apart from MASLD and its disease-defining conditions, many other metabolic diseases, such as chronic kidney disease, heart failure and stroke, share common pathophysiological mechanisms, and it was recently suggested to adopt a new staging structure called cardiovascular–kidney–metabolic (CKM) syndrome, highlighting a multi-system disorder to enhance prevention, risk stratification and multidisciplinary management of these intercalated conditions.[9] There are five stages that encompass the spectrum of risk and window for intervention: stage 0, no CKM risk factors; stage I, excess or dysfunctional adiposity; stage II, metabolic risk factors; stage III, subclinical cardiovascular disease and stage IV, clinical cardiovascular disease. It is worth highlighting the prominent role of adiposity in CKM syndrome, for the fact that adipose tissue is recognized as an active endocrine organ that contributes to inflammation and metabolic dysfunction.[10] When considering MASLD in the context of CKM syndrome, more patients with

MASLD fell into CKM stage II or III but not stage IV compared with the general population, as shown in a retrospective analysis of the National Health and Nutrition Examination Survey (NHANES) 2017–2020 and NHANES III cohorts.[11] The prevalence of advanced liver fibrosis defined by FIB-4 >2.67 was 0.00%, 4.35%, 17.28%, 40.24% and 38.12% for CKM stage 0, I, II, III and IV, respectively.[11] Similar multispecialty practice recommendations for complex conditions involving diabetes, cardiorenal and/or metabolic diseases have been recently updated and expanded for stratified assessments and targeted treatment plans for the 'hepato-adipo-cardio-renal axis', and some have even proposed a new term, 'cardiovascular–renal–hepatic–metabolic' (CRHM) syndrome.[12,13] In fact, the liver is recognized for its role in insulin resistance, lipid metabolism, endothelial dysfunction and systemic inflammation, and therefore should be repositioned at the centre of CKM syndrome (i.e. liver–CKM).[13,14] Emerging research has looked into the pathogenesis of liver–CKM, exemplified by an interesting commentary by Wimalarathne et al., which proposed a novel link between clonal haematopoiesis of indeterminate potential (CHIP), an age-related phenomenon, and driving systemic inflammation, which also increases the risk of metabolic dysfunction-associated steatohepatitis and fibrosis, elucidating the role of CHIP in the progression of liver–CKM syndrome.[15] Overall, MASLD is a manifestation of a broader clinical syndrome (be it CKM, liver–CKM or CRHM), and treatments targeting the underpinning metabolic dysfunction are needed for reduction of all-cause mortality in patients with MASLD, considering the fact that cardiovascular disease and extrahepatic malignancies remain the leading causes of death among people living with MASLD.[1,16,17]

Beyond MASLD, metabolic dysfunction is frequently seen in patients with other chronic liver conditions. In chronic hepatitis B infection, both body mass index and T2D have been implicated in fibrosis progression, of which adipokines, including adipocyte fatty acid-binding protein and fibroblast growth factor 21, have been implicated.[18–20] Concomitant hepatic steatosis, as a manifestation of metabolic dysfunction, is observed in 47.8% and is associated with fibrosis progression and hepatitis B surface antigen seroclearance.[21,22] The number of cardiometabolic risk factors, instead of hepatic steatosis *per se*, was associated with all-cause and liver-specific mortality.[23] The high prevalence of concomitant chronic hepatitis B infection and MASLD, together with accumulating data on its clinical implications, has sparked interest among some researchers, who proposed a novel entity of metabolic dysfunction superimposed with chronic hepatitis B infection (Met-HBV) that awaits further evaluation.[24] In patients with primary biliary cholangitis, concomitant MASLD was associated with worse prognosis in terms of inadequate biochemical response to ursodeoxycholic acid treatment by Paris II criteria (61.1% versus 33.3%; p=0.004) and higher liver-related mortality or liver transplantation (22% versus 7.5%; p=0.03).[25] In patients who have undergone liver transplantation, *de novo* hepatic steatosis was found in one-quarter of patients and was associated with graft dysfunction.[26] Having concomitant aetiologies of chronic liver disease in MASLD has been shown to increase the risk of extrahepatic cancers and cancer-related mortality in a non-linear manner.[27] These examples call for more research in patients with all types of chronic liver disease having concomitant metabolic dysfunction and/or hepatic steatosis. For instance, it should be considered to remove the exclusion criteria of concomitant MASLD in clinical trials for chronic hepatitis B infection.

In summary, metabolic dysfunction represents a key pathogenic and prognostic factor in MASLD and other chronic liver diseases. In patients with any evidence of metabolic dysfunction, MASLD should be actively sought using imaging, followed by non-invasive tests for risk stratification. The clinical syndromes incorporating the liver and other metabolic diseases provide a useful framework for healthcare professionals to acknowledge their implications, streamline management strategies and explore new treatment targets. ❑

1. Younossi ZM, Golabi P, Paik JM, et al. The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): A systematic review. *Hepatology*. 2023;77:1335–47. DOI: 10.1097/HEP.0000000000000004.
2. Wong RJ, Aguilar M, Cheung R, et al. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. *Gastroenterology*. 2015;148:547–55. DOI: 10.1053/j.gastro.2014.11.039.
3. Rinella ME, Lazarus JV, Ratziu V, et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. *J Hepatol*. 2023;79:1542–56. DOI: 10.1016/j.jhep.2023.06.003.
4. Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: A joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*. 2009;120:1640–5. DOI: 10.1161/CIRCULATIONAHA.109.192644.
5. Huang DQ, Noureddin N, Ajmera V, et al. Type 2 diabetes, hepatic decompensation, and hepatocellular carcinoma in patients with non-alcoholic fatty liver disease: An individual participant-level data meta-analysis. *Lancet Gastroenterol Hepatol*. 2023;8:829–36. DOI: 10.1016/S2468-1253(23)00157-7.
6. Tamaki N, Kimura T, Wakabayashi S-I, et al. Cardiometabolic criteria as predictors and treatment targets of liver-related events and cardiovascular events in metabolic dysfunction-associated steatotic liver disease. *Aliment Pharmacol Ther*. 2024;60:1033–41. DOI: 10.1111/apt.18205.
7. Lam SM, Wang Z, Song JW, et al. Non-invasive lipid panel of MASLD fibrosis transition underscores the role of lipoprotein sulfatides in hepatic immunomodulation. *Cell Metab*. 2025;37:69–86. DOI: 10.1016/j.cmet.2024.09.009.
8. Xu C, Wang K, Peng Z, et al. Association between high-sensitivity c-reactive protein levels and metabolic dysfunction-associated steatotic liver disease and liver fibrosis risk: A study based on NHANES data. *Turk J Gastroenterol*. 2025;36:590–9. DOI: 10.5152/tjg.2025.24251.
9. Ndumele CE, Rangaswami J, Chow SL, et al. Cardiovascular-kidney-metabolic health: A presidential advisory from the American Heart Association. *Circulation*. 2023;148:1606–35. DOI: 10.1161/CIR.0000000000001184.
10. Kershaw EE, Flier JS. Adipose tissue as an endocrine organ. *J Clin Endocrinol Metab*. 2004;89:2548–56. DOI: 10.1210/jc.2004-0395.
11. Yang T, Bu T, Yang B, et al. CKM: A new approach to managing metabolic comorbidities in MASLD? *J Hepatol*. 2025;82:e291–2. DOI: 10.1016/j.jhep.2024.12.014.
12. Handelsman Y, Anderson JE, Bakris GL, et al. DCRM 2.0: Multispecialty practice recommendations for the management of diabetes, cardiorenal, and metabolic diseases. *Metabolism*. 2024;159:155931. DOI: 10.1016/j.metabol.2024.155931.
13. Theodorakis N, Nikolaou M. From cardiovascular-kidney-metabolic syndrome to cardiovascular-renal-hepatic-metabolic syndrome: Proposing an expanded framework. *Biomolecules*. 2025;15:213. DOI: 10.3390/biom15020213.
14. Goodheart RH, Ayonrinde OT. Connecting the dots: Hepatic steatosis as a central player in the choreography of the liver-cardiovascular-kidney-metabolic syndrome. *Heart Lung Circ*. 2025;34:1050–9. DOI: 10.1016/j.hlc.2025.08.009.
15. Wimalarathne S, Lan NSR, Adams LA, Dwivedi G. Clonal haematopoiesis and cardiovascular-kidney-metabolic syndrome: Emerging links. *Heart Lung Circ*. 2025;34:991–4. DOI: 10.1016/j.hlc.2025.05.100.
16. Angulo P, Kleiner DE, Dam-Larsen S, et al. Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease. *Gastroenterology*. 2015;149:389–97. DOI: 10.1053/j.gastro.2015.04.043.
17. Adams LA, Harmsen S, St Sauver JL, et al. Nonalcoholic fatty liver disease increases risk of death among patients with diabetes: A community-based cohort study. *Am J Gastroenterol*. 2010;105:1567–73. DOI: 10.1038/ajg.2010.18.
18. Seto WK, Fung J, Cheung K-S, et al. Body-mass index is associated with fibrosis regression during long-term nucleoside analogue therapy in chronic hepatitis B. *Aliment Pharmacol Ther*. 2016;44:1071–9. DOI: 10.1111/apt.13804.
19. Mak LY, Hui RW, Lee CH, et al. Glycemic burden and the risk of adverse hepatic outcomes in patients with chronic hepatitis B with type 2 diabetes. *Hepatology*. 2023;77:606–18. DOI: 10.1002/hep.32716.
20. Mak LY, Lee CH, Cheung KS, et al. Association of adipokines with hepatic steatosis and fibrosis in chronic hepatitis B patients on long-term nucleoside analogue. *Liver Int*. 2019;39:1217–25. DOI: 10.1111/liv.14104.
21. Mak LY, Yuen MF, Seto WK. Letter regarding "A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement". *J Hepatol*. 2020;73:1573–4. DOI: 10.1016/j.jhep.2020.07.008.
22. Mak LY, Hui RW, Fung J, et al. Diverse effects of hepatic steatosis on fibrosis progression and functional cure in virologically quiescent chronic hepatitis B. *J Hepatol*. 2020;73:800–6. DOI: 10.1016/j.jhep.2020.05.040.
23. Huang SC, Su TH, Tseng TC, et al. All-cause and cause-specific mortality in patients with chronic hepatitis B and concurrent steatotic liver disease. *J Hepatol*. 2025;83:43–51. DOI: 10.1016/j.jhep.2024.12.009.
24. AASLD Liver Learning. Met-HBV: Diagnosis and Management with MASLD in Patients with Chronic HBV Infection. 2026. Available at: liverlearning.aasld.org/Listing/Met-HBV-Diagnosis-and-Management-with-MASLD-in-Patients-with-Chronic-HBV-Infection-17801 (accessed: 29 January 2026).
25. Hernández-Pérez M, Riado D, Pena E, et al. The overlap with metabolic dysfunction-associated steatotic liver disease negatively affects outcomes of primary biliary cholangitis. *Aliment Pharmacol Ther*. 2024;60:613–9. DOI: 10.1111/apt.18134.
26. Mak LY, Chan AC, Wong TC, et al. High prevalence of de novo metabolic dysfunction-associated fatty liver disease after liver transplantation and the role of controlled attenuation parameter. *BMC Gastroenterol*. 2023;23:307. DOI: 10.1186/s12876-023-02940-y.
27. Chung GE, Yu SJ, Yoo J, et al. Differential risk of 23 site-specific incident cancers and cancer-related mortality among patients with metabolic dysfunction-associated fatty liver disease: A population-based cohort study with 9.7 million Korean subjects. *Cancer Commun*. 2023;43:863–76. DOI: 10.1002/cac2.12454.