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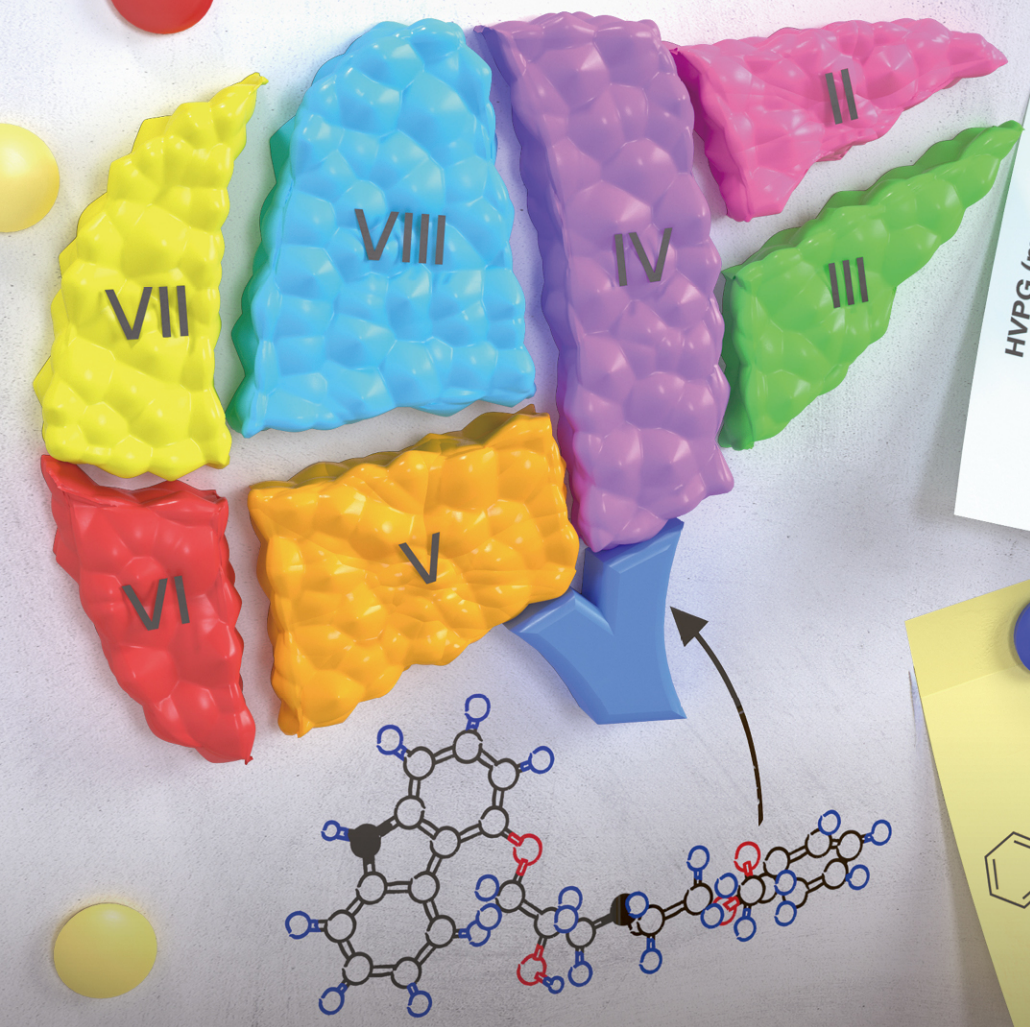

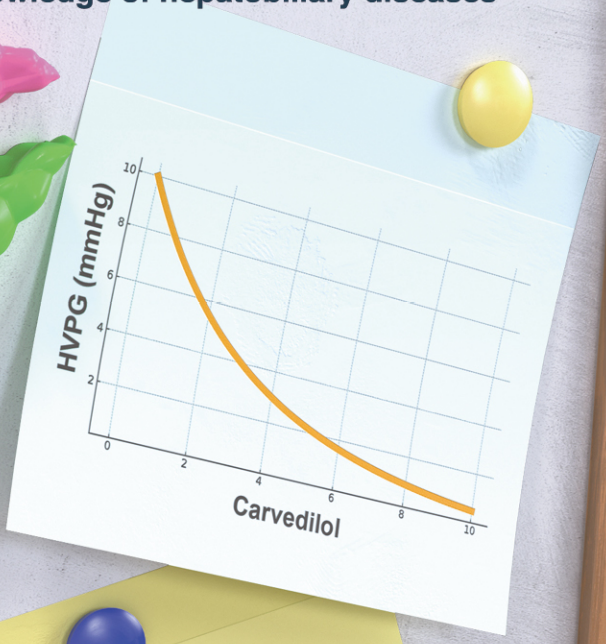

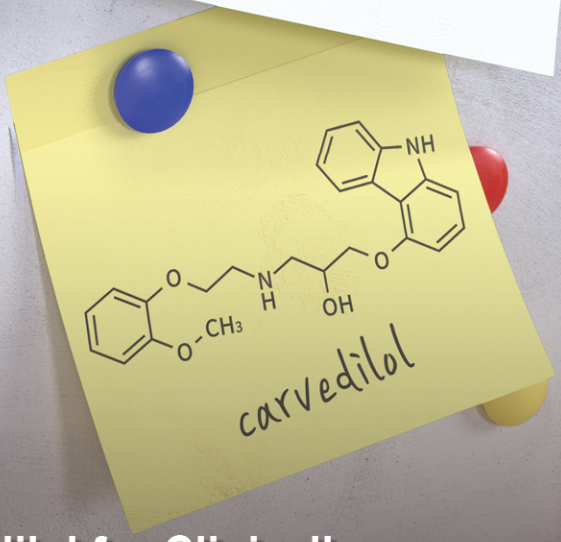

Non-invasive Model guiding Carvedilol for Clinically Significant Portal HTN

Intrapatient variability of tacrolimus on CKD in LT
HCV self-testing and disease burden reduction
MASLD and microbiota
Bariatric surgery for metabolic cirrhosis

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Editorial

Spotting undiagnosed significant liver fibrosis in the general population: impact on subsequent clinical care: Editorial on "Prevalence of clinically significant liver fibrosis in the general population: A systematic review and meta-analysis"

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Data from the World Health Organization and Global Burden of Disease suggest the prevalence of chronic liver diseases (CLD) has been increasing in recent years,[1] placing heavy clinical, economic, and patient-experience burdens globally. Metabolic dysfunction-associated steatotic liver disease (MASLD) is currently the most common CLD, impacting around 30% of the adult population across the globe.[2] Chronic viral hepatitis B and C infections affect around 350 million people worldwide and are still leading etiologies of cirrhosis and liver cancer.[3,4] Meanwhile, alcohol-related liver disease leads to a fast-growing burden of cirrhosis and related complications.[5] The morbidity and mortality associated with CLD have been posing a significant threat to global health. Chronic liver inflammation leads to excessive extracellular matrix protein production, resulting in the formation of hepatic fibrosis over time, which is the most important determinant of liver-related complications including hepatic decompensation and hepatocellular carcinoma (HCC) regardless of liver disease etiologies.

Previous studies demonstrated that the risk of liver-related mortality increased exponentially with the stage of fibrosis, with a more prominent rise starting from significant liver fibrosis.[6,7] Significant liver fibrosis is thus an important target for detection,[8] which can facilitate subsequent specialist referrals and allow effective medical interventions or lifestyle modifications to be implemented before the onset of cirrhosis. Prospective evidence has confirmed the histological benefit associated with dietary and lifestyle interventions in patients with MASLD.[9] However, owing to nonspecific symptoms in the early stage of liver diseases, low

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awareness of patients at risk for progression, coupled with the lack of reliable diagnostic or screening modalities in the general population, patients' diagnosis can be delayed for years until cirrhosis is established.[10] Only when our system accurately identifies patients at risk of poor prognosis, can we implement timely intervention, thereby delivering tangible benefits to the broader population. The first and foremost step is to comprehend the prevalence of clinically significant liver fibrosis in the general population. Although liver biopsy remains the gold standard for diagnosing liver fibrosis, its invasive nature precludes its widespread use. Detecting liver fibrosis among the general public would rely on noninvasive tests (NITs).

In this issue of *Clinical and Molecular Hepatology*, Kim et al.[11] assessed the pooled prevalence of clinically significant liver fibrosis with NITs in the general population. They conducted a systematic review and meta-analysis in the MEDLINE (OVID), EMBASE, the Cochrane Library, and KoreaMed, targeting English-language articles published from their inception until June 13, 2023, focusing on cohort studies reporting the prevalence of liver fibrosis using NITs in asymptomatic adults or those in primary care settings. Statistical heterogeneity was assessed using the I^2 statistic, which estimates the percentage of total variation across the included studies attributable to heterogeneity rather than sampling error, with an I^2 value greater than 50% indicating substantial heterogeneity.[12] To explore the sources of heterogeneity, they performed subgroup analyses based on the types of NIT, stage of fibrosis, and geographical regions.

After initially identifying 6,429 records, they found 45 studies eligible for inclusion, encompassing 566,160 participants, with the NITs used being the fibrosis-4 (FIB-4) index in 13 studies, vibration-controlled transient elastography (VCTE) in 27 studies, FibroTest® in two studies, nonalcoholic fatty liver disease fibrosis score (NFS) in one study, and magnetic resonance elastography (MRE) in two studies. Of these, 41 studies scored greater than 70% according to the Joanna Briggs Institute's (JBI) critical appraisal tool, indicating good study quality.

Given the sufficient data and substantial heterogeneity of the included studies, meta-analyses using random effect models were conducted for both the FIB-4 index and liver stiffness measurement (LSM) by VCTE. The pooled prevalence of significant fibrosis (≥F2) in the general population assessed by LSM with a cutoff between 5.9 and 9.6 kPa was 7.3% across 22 studies (n=56,969). Regionally, this rate was 10.7% in the Americas, 6.1% in Europe, and 7.1% in the Western Pacific region. Regarding advanced fibrosis (≥F3), the pooled prevalence determined by FIB-4 index (mainly using a cutoff of 2.67) was 2.3% across 13 studies (n=509,191), with regional prevalence of 4.3% in the Americas, 2.2% in Europe, and 1.3% in the Western Pacific. The pooled prevalence of ≥F3 detected by LSM with a cutoff between 8–10 kPa was 3.5% across 15 studies (n=45,395). The regional rate was 5.8% in the Americas, 3.1% in Europe, and 2.4% in the Western Pacific. Lastly, the pooled prevalence of liver cirrhosis, based on LSM with a cutoff between 10.3 and 15 kPa, was 1.2% in the general population (14 studies; n=38,232). The authors also documented the prevalence of liver fibrosis diagnosed using FibroTest, NFS, and MRE, but based on a limited number of studies.

The study by Kim et al.[11] provides a valuable reference for enhancing understanding regarding the prevalence of CLD in the general population, highlighting the importance of early detection of clinically significant liver fibrosis. However, some limitations in the study should be noted. Firstly, high heterogeneity can be observed in the analysis of the prevalence of advanced liver fibrosis using FIB-4 index, and the analyses of different stages of fibrosis using VCTE. The most obvious source of heterogeneity is the use of different cut-offs in individual studies to define fibrosis and cirrhosis. The authors tried to resolve the bias by the leave-one-out sensitivity analyses to confirm that the results were not significantly influenced by a single study. However, it might not easily mitigate the impact of heterogeneous cut-offs used across different studies. Another issue arising from the heterogeneity is the notably elevated prevalence of fibrosis and cirrhosis in the Americas, which were the highest among all regions. The discordant findings in com-

Abbreviations:

CLD, chronic liver diseases; ELF, enhanced liver fibrosis; FIB-4, fibrosis-4; HCC, hepatocellular carcinoma; JBI, Joanna Briggs Institute; LSM, liver stiffness measurement; MASLD, metabolic dysfunction-associated steatotic liver disease; MRE, magnetic resonance elastography; NFS, nonalcoholic fatty liver disease fibrosis score; NIT, noninvasive test; VCTE, vibration-controlled transient elastography

parison to existing studies suggest that the study population may not entirely represent the broader general population.[13,14] Heterogeneity between studies can only be partly addressed through subgroup analyses of regions, as the value of I^2 is still over 50% within subgroups. Additionally, significant differences in age, the prevalence of metabolic risk factors (including obesity, dyslipidemia and type 2 diabetes mellitus), and other CLD (including hepatitis B or C and MASLD) can also be observed between studies, revealing other potential sources of heterogeneity. Owing to the variations among the included studies, the results of this article should be interpreted carefully. Secondly, the inconsistency of defining the general population across studies possibly introduces bias in the study population selection. Furthermore, the absence of data concerning key clinical characteristics in some studies like age, obesity, alcohol consumption, and lifestyle habits, all significant risk factors for CLD, could affect the interpretation of the composition and representativeness of individual study populations.[14] Last but not least, although assessing publication bias is not mandatory in meta-analyses of proportion,[15] additional investigations and further qualitative descriptions are warranted, particularly in studies exhibiting significant heterogeneity. Overall, the study's limitations in high heterogeneity, participant selection and the lack of comprehensive data on risk factors underscore the need for more cohort studies in the general background.

While LSM by VCTE offers a more accurate quantification of liver fibrosis, serum-based fibrosis tests such as the FIB-4 index remain an important first step of screening given the better accessibility and high negative predictive value in excluding patients without advanced liver fibrosis. While patients with a high FIB-4 index can be referred to the hepatology clinic, those with an intermediate FIB-4 index would deserve a second liver-specific test, such as LSM by VCTE or enhanced liver fibrosis (ELF) (Fig. 1). Although MASLD is prevalent in the general population, the meta-analysis by Kim et al.[11] demonstrated that only a minority of individuals in the general population have significant or advanced liver fibrosis. This highlights the importance of selecting at-risk populations for fibrosis screening, which can include individuals with type 2 diabetes mellitus,[16] hepatic steatosis, obesity with cardiometabolic risk factors, and those with persistently elevated liver enzymes.[9,17] Based on this concept, different clinical care pathways have been established to facilitate case identification and early referral and intervention.[9,17-19] A good implementation of the pathways would rely on the mutual agreement between hepatologists, primary care physicians, endocrinologists and other specialists on the importance of case identification, improving public awareness, and the additional effort to arrange relevant investigations

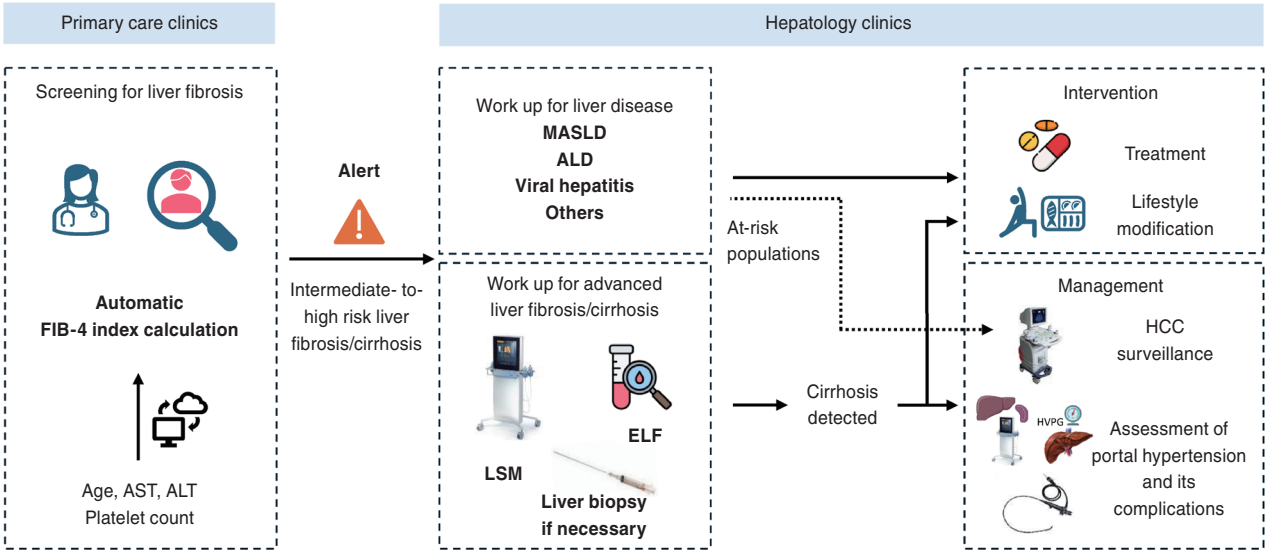

Figure 1. Care pathway for detection of advanced liver disease in the general population. FIB-4, Fibrosis-4; AST, aspartate aminotransferase; ALT, alanine aminotransferase; MASLD, metabolic dysfunction-associated steatotic liver disease; LSM, liver stiffness measurement; ELF, enhanced liver fibrosis; HCC, hepatocellular carcinoma.

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and follow-up on abnormal results,[20] ultimately resulting in improving clinical outcomes of our patients and alleviating the burden on our society.

Authors' contribution

All authors were responsible for the interpretation of data, the drafting, and the critical revision of the manuscript for important intellectual content. All authors approved the final version of the article.

Conflicts of Interest

Terry Yip has served as an advisory committee member and a speaker for Gilead Sciences. The other authors declare that they have no competing interests.

REFERENCES

1. Younossi ZM, Wong G, Anstee QM, Henry L. The global burden of liver disease. Clin Gastroenterol Hepatol 2023;21:1978-1991.
2. Yip TC, Vilar-Gomez E, Petta S, Yilmaz Y, Wong GL, Adams LA, et al. Geographical similarity and differences in the burden and genetic predisposition of NAFLD. Hepatology 2023;77:1404-1427.
3. Polaris Observatory Collaborators. Global prevalence, cascade of care, and prophylaxis coverage of hepatitis B in 2022: a modelling study. Lancet Gastroenterol Hepatol 2023;8:879-907.
4. Martinello M, Solomon SS, Terrault NA, Dore GJ. Hepatitis C. Lancet 2023;402:1085-1096.
5. Huang DQ, Mathurin P, Cortez-Pinto H, Loomba R. Global epidemiology of alcohol-associated cirrhosis and HCC: trends, projections and risk factors. Nat Rev Gastroenterol Hepatol 2023;20:37-49.
6. Dulai PS, Sirlin CB, Loomba R. MRI and MRE for non-invasive quantitative assessment of hepatic steatosis and fibrosis in NAFLD and NASH: clinical trials to clinical practice. J Hepatol 2016;65:1006-1016.
7. Hagström H, Nasr P, Ekstedt M, Hammar U, Stål P, Hultcrantz R, et al. Fibrosis stage but not NASH predicts mortality and time to development of severe liver disease in biopsy-proven NAFLD. J Hepatol 2017;67:1265-1273.
8. Li G, Lin H, Sripongpun P, Liang LY, Zhang X, Wong VWS, et al. Diagnostic and prognostic performance of the SAFE score in non-alcoholic fatty liver disease. Liver Int 2024;44:15-26.
9. European Association for the Study of the Liver (EASL); European Association for the Study of Obesity (EASO); European Association for the Study of the Liver (EASL). EASL-EASD-EASO clinical practice guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). J Hepatol 2024;81:492-542.
10. Ratziu V, Cadranel JF, Serfaty L, Denis J, Renou C, Delassalle P, et al. A survey of patterns of practice and perception of NAFLD in a large sample of practicing gastroenterologists in France. J Hepatol 2012;57:376-383.
11. Kim HY, Yu JH, Chon YE, Kim SU, Kim MN, Han JW, et al. Prevalence of clinically significant liver fibrosis in the general population: a systematic review and meta-analysis. Clin Mol Hepatol 2024;30(Suppl):S199-S213.
12. Deeks JJ, Higgins JP, Altman DG, Cochrane Statistical Methods Group. Analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. eds. Cochrane Handbook for Systematic Reviews of Interventions. 2nd ed. Hoboken: Wiley-Blackwell, 2019:241-284.
13. GBD 2017 Cirrhosis Collaborators. The global, regional, and national burden of cirrhosis by cause in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Gastroenterol Hepatol 2020;5:245-266.
14. Huang DQ, Terrault NA, Tacke F, Gluud LL, Arrese M, Bugianesi E, et al. Global epidemiology of cirrhosis - aetiology, trends and predictions. Nat Rev Gastroenterol Hepatol 2023;20:388-398.
15. Barker TH, Migliavaca CB, Stein C, Colpani V, Falavigna M, Aromataris E, et al. Conducting proportional meta-analysis in different types of systematic reviews: a guide for synthesisers of evidence. BMC Med Res Methodol 2021;21:189.
16. Zhang X, Yip TC, Tse YK, Hui VW, Li G, Lin H, et al. Duration of type 2 diabetes and liver-related events in nonalcoholic fatty liver disease: a landmark analysis. Hepatology 2023;78:1816-1827.
17. Kanwal F, Shubrook JH, Adams LA, Pfotenhauer K, Wai-Sun Wong V, Wright E, et al. Clinical care pathway for the risk stratification and management of patients with nonalcoholic fatty liver disease. Gastroenterology 2021;161:1657-1669.
18. Chan WK, Treeprasertsuk S, Goh GB, Fan JG, Song MJ, Charatcharoenwitthaya P, et al. Optimizing use of nonalcoholic fatty liver disease fibrosis score, fibrosis-4 score, and liver stiff-

ness measurement to identify patients with advanced fibrosis. Clin Gastroenterol Hepatol 2019;17:2570-2580.e37.
19. Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, Abdelmalek MF, Caldwell S, Barb D, et al. AASLD practice guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology 2023;77:1797-1835.
20. Zhang X, Yip TC, Wong GL, Leow WX, Liang LY, Lim LL, et al. Clinical care pathway to detect advanced liver disease in patients with type 2 diabetes through automated fibrosis score calculation and electronic reminder messages: a randomised controlled trial. Gut 2023;72:2364-2371.

https://doi.org/10.3350/cmh.2024.0737