[6] **Niehaus CE**, **Strunz B**, Cornillet M, Falk CS, Schnieders A, Maasoumy B, et al. MAIT cells are enriched and highly functional in ascites of patients with decompensated liver cirrhosis. Hepatology 2020;72:1378–1393.
[7] **Marjot T**, **Eberhardt CS**, **Boettler T**, Belli LS, Berenguer M, Buti M, et al. Impact of COVID-19 on the liver and on the care of patients with chronic liver disease, hepatobiliary cancer, and liver transplantation: an updated EASL position paper. J Hepatol 2022;77(4):1161–1197.
[8] Krassenburg LAP, Maan R, Ramji A, Manns MP, Cornberg M, Wedemeyer H, et al. Clinical outcomes following DAA therapy in patients with HCV-related cirrhosis depend on disease severity. J Hepatol 2021;74:1053–1063.
[9] Cornberg M, Buti M, Eberhardt CS, Grossi PA, Shouval D. EASL position paper on the use of COVID-19 vaccines in patients with chronic liver diseases, hepatobiliary cancer and liver transplant recipients. J Hepatol 2021;74:944–951.
[10] Cornberg M, Eberhardt CS. Protected or not protected, that is the question - first data on COVID-19 vaccine responses in patients with NAFLD and liver transplant recipients. J Hepatol 2021;75:265–266.

Relationship between non-alcoholic fatty liver disease and atrial fibrillation: Assessment of latest evidence

To the Editor:

We read with great interest the study by van Kleef *et al.*, which suggested that higher liver stiffness instead of ultrasonography-diagnosed hepatic steatosis was significantly correlated with atrial fibrillation (AF).[1] We believe that this study provided the most current evidence to improve the management of cardiovascular risk in patients with fatty liver disease; however, there are some issues worth discussing.

First, the relatively low incidence rate of AF (10.2 per 1,000 person-years) in this study may result in an inability to detect a modest association between hepatic steatosis and AF. Second, the study population was older and had a high prevalence of chronic comorbidities such as hypertension and diabetes. Although these factors were adjusted for in the study, older people and individuals with diabetes or hypertension are more likely to be treated with a range of medications that may reduce the risk of cardiovascular diseases including AF. The information on the use of these medications was missing in the study. Not only that, but there was also a higher risk of developing incident type 2 diabetes and hypertension in patients with non-alcoholic fatty liver disease (NAFLD),[2] the current study only screened for these comorbidities at baseline, and data on the occurrence of comorbidities during the follow-up period were not available. Finally, the relatively short follow-up period may contribute to some AF cases being missed.

We also noticed another recent large prospective population-based cohort study that identified NAFLD based on fatty liver index (FLI) and indicated NAFLD being positively correlated with AF risk.[3] These divergent results might be attributed to differences in study populations, study designs, covariate adjustments, and different diagnostic methods for NAFLD. The relationship between FLI and increased AF risk might be due to the metabolically unhealthy components of FLI. Moreover, the current European guidelines recommend imaging modalities rather than non-invasive scoring as first-line diagnostic tools for steatosis in clinical practice.[4]

Thus, to further evaluate the association of the diseases, we conducted a meta-analysis that investigated the associations between imaging-identified NAFLD and AF risk. The literature search was performed using PubMed, Embase, and Web of Science to identify all relevant articles until 20 July 2022. The following studies were included: (1) cohort studies of adult participants (≥18 years) that reported the association between NAFLD and AF risk; (2) studies in which the diagnosis of NAFLD was imaging (mainly ultrasound) based, excluding other competing causes of chronic liver disease (such as heavy alcohol consumption); (3) studies that quantified the outcome with multivariable-adjusted effect estimates (odds ratios [ORs]), relative risks [RRs], or hazard ratios [HRs]) with the corresponding 95% CIs. The methodological quality of the included studies was evaluated based on the Newcastle-Ottawa Quality Assessment Scale. To further eliminate confounding factors, the adjusted RRs and 95% CIs were extracted for the analyses. The reported HRs were considered equal to RRs, and ORs were converted to RRs according to the method given by Zhang *et al.*[5] A random-effects model was used if interstudy heterogeneity existed.

Four high quality prospective cohort studies involving 9,243 participants were selected.[1,6–8] The combined results showed no significant difference in the risk of AF between individuals with imaging-defined NAFLD and those without NAFLD after multivariable adjustment (RR = 1.38, 95% CI 0.81−2.35; p = 0.234; Fig. 1A), with significant heterogeneity among studies (I^2 = 72.9%, p = 0.011). Subsequently, we performed another meta-analysis by pooling the minimally adjusted RRs (adjusted for sex and age), and the results demonstrated that NAFLD was not associated with an increased risk of AF without adjusting for other cardiovascular risk factors (RR 1.43, 95% CI 0.90−2.28; p = 0.131; I^2 = 75.1%; Fig. 1B). Among the four included studies, three used ultrasonography to diagnose fatty liver and the fourth used computed tomography. The non-significant association we observed between NAFLD and the risk of incident AF was consistent for different NAFLD definitions. The subgroup analysis indicated significantly increased AF risk in the subgroup of 'sample <2,000,' while no significant association was observed in the subgroups of 'general population' and 'sample ≥2,000.' Additionally, a sensitivity analysis conducted by removing individual studies at a time revealed that the results were not materially altered.

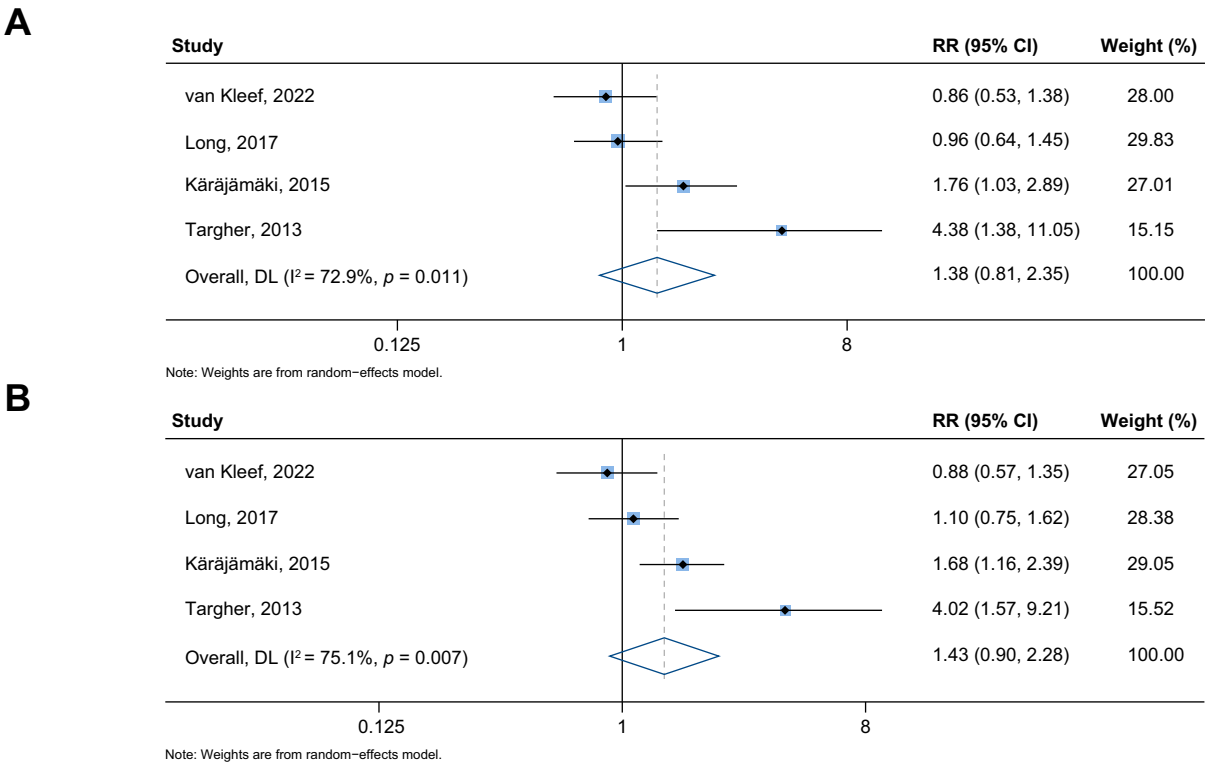

Fig. 1. Forest plots showing the association between imaging-defined non-alcoholic fatty liver disease and the risk of atrial fibrillation. Association in the (A) multivariable-adjusted model and (B) minimally adjusted model. RR, relative risk.

Unlike most of the previous meta-analyses,[9,10] this meta-analysis reported that there was no significant association between imaging-defined NAFLD and the risk of AF. However, the result should be cautiously interpreted. First, although multivariate-adjusted estimates were reported in all studies, the adjustment factors were not consistent among these studies and several unaccounted confounders existed, which may have contributed to the high heterogeneity among these studies. Second, although only the imaging-based studies were included, ultrasonography or computed tomography have high sensitivity and specificity only for moderate-to-severe steatosis.[2] Meanwhile, AF diagnosis based on standard electrocardiograms may miss some patients with paroxysmal AF. Further longitudinal studies with accurate standardized definitions of steatosis and AF are needed to determine strong evidence of the independent association between the two diseases.

Tianyi Ma
Xiaohui Yu
Mei Sun*
Department of Gastroenterology and Hepatology, The Central Hospital of Dalian University of Technology, Dalian 116000, China
*Corresponding author. Address: Department of Gastroenterology and Hepatology, The Central hospital of Dalian University of Technology, No. 826 Xinan Road, Dalian, Liaoning province, China. Tel.: +86041184412001, fax: +86041184411941.
E-mail address: drsunmei75@163.com (M. Sun)

Received 8 August 2022; Accepted 11 August 2022; Available online 21 August 2022
https://doi.org/10.1016/j.jhep.2022.08.014

Financial support

The authors received no financial support to produce this manuscript.

Conflicts of interest

The authors declare that they have no competing interests.
Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Tianyi Ma conceived of the original idea and prepared the initial version of this manuscript. Xiaohui Yu and Mei Sun critically revised the manuscript. All authors read and approved the final manuscript.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2022.08.014.

References

Author names in bold designate shared co-first authorship.

[1] van Kleef LA, Lu Z, Arfan Ikram M, de Groot NMS, Kavousi M, de Knegt RJ. Liver stiffness not fatty liver disease is associated with atrial fibrillation: the Rotterdam study. J Hepatol 2022;77:931–938. https://doi.org/10.1016/j.jhep.2022.05.030.
[2] European Association for the Study of the Liver. European association for the study of diabetes, European association for the study of obesity. EASL-

EASD-EASO clinical practice guidelines for the management of non-alcoholic fatty liver disease. J Hepatol 2016;64:1388–1402. https://doi.org/10.1016/j.jhep.2015.11.004.
[3] **Choi J**, **Lee SR**, Choi EK, Ahn HJ, Kwon S, Park SH, et al. Non-alcoholic fatty liver disease and the risk of incident atrial fibrillation in young adults: a nationwide population-based cohort study. Front Cardiovasc Med 2022;9:832023. https://doi.org/10.3389/fcvm.2022.832023.
[4] European Association for the Study of the Liver. EASL Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis - 2021 update. J Hepatol 2021;75:659–689. https://doi.org/10.1016/j.jhep.2021.05.025.
[5] Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. JAMA 1998;280:1690–1691. https://doi.org/10.1001/jama.280.19.1690.
[6] Long MT, Yin X, Larson MG, Ellinor PT, Lubitz SA, McManus DD, et al. Relations of liver fat with prevalent and incident atrial fibrillation in the framingham heart study. J Am Heart Assoc 2017;6:e005227. https://doi.org/10.1161/JAHA.116.005227.
[7] **Käräjämäki AJ**, **Pätsi OP**, Savolainen M, Kesäniemi YA, Huikuri H, Ukkola O. Non-alcoholic fatty liver disease as a predictor of atrial fibrillation in middle-aged population (OPERA study). PLoS One 2015;10:e0142937. https://doi.org/10.1371/journal.pone.0142937.
[8] Targher G, Valbusa F, Bonapace S, Bertolini L, Zenari L, Rodella S, et al. Non-alcoholic fatty liver disease is associated with an increased incidence of atrial fibrillation in patients with type 2 diabetes. PLoS One 2013;8:e57183. https://doi.org/10.1371/journal.pone.0057183.
[9] **Alon L**, **Corica B**, Raparelli V, Cangemi R, Basili S, Proietti M, et al. Risk of cardiovascular events in patients with non-alcoholic fatty liver disease: a systematic review and meta-analysis. Eur J Prev Cardiol 2022;29:938–946. https://doi.org/10.1093/eurjpc/zwab212.
[10] Gong H, Liu X, Cheng F. Relationship between non-alcoholic fatty liver disease and cardiac arrhythmia: a systematic review and meta-analysis. J Int Med Res 2021;49:3000605211047074. https://doi.org/10.1177/0300060521047074.

Accuracy of transient elastography in assessing fibrosis at diagnosis in individuals with autoimmune liver disease

To the Editor:

Recently, this *Journal* published a large, multi-center, longitudinal cohort study by Corpechot *et al.*, which validated the prognostic value of baseline liver stiffness (LS) by vibration-controlled transient elastography (VCTE) in individuals with primary biliary cholangitis (PBC). LS also improved the prognostic performance of established biochemical markers of treatment response.[1]

The study has directly supported the inclusion of baseline LS in prognostic tools developed for PBC. Interestingly, results from our meta-analysis regarding the diagnostic performance of LS for autoimmune liver disease (AILD) also provided indirect explanation for its prognostic role, considering baseline histological fibrosis is an independent predictor of disease progression and clinical outcomes in individuals with AILD.[2,3]

Of the 754 articles identified through the systematic search, a total of 44 studies published from 2006 to 2021 including 3,488 participants with AILD were finally enrolled. Taking liver biopsy as standard, we explored the diagnostic ability of 11 non-invasive markers of fibrosis in subgroups of individuals with autoimmune hepatitis (AIH) (n = 1,253), PBC (n = 1,734) and primary sclerosing cholangitis (PSC) (n = 501). Moreover, considering genetic and environmental factors can contribute to the development and progression of AILD, both Asian and European populations were covered in our study[4] (Table S1). Our results indicated that LS by transient elastography had a remarkable diagnostic performance compared to other non-invasive biomarkers of liver fibrosis (Table S2). Moreover, LS performed better for the diagnosis of PBC than AIH. LS had an excellent diagnostic accuracy in detecting liver fibrosis with summary area under ROC curves (AUROCs) of 0.94, 0.92 and 0.93 for significant fibrosis (SF), advanced fibrosis (AF) and cirrhosis, respectively, in individuals with PBC. While LS had a moderate to excellent accuracy with summary AUROCs of 0.83, 0.91 and 0.90 in individuals with AIH (Fig. 1). Liver histology predicts fibrosis progression and cirrhosis development in individuals with AILD; thus, the higher consistency between LS and liver histopathology in individuals with PBC can provide further support for Corpechot *et al.*'s findings.

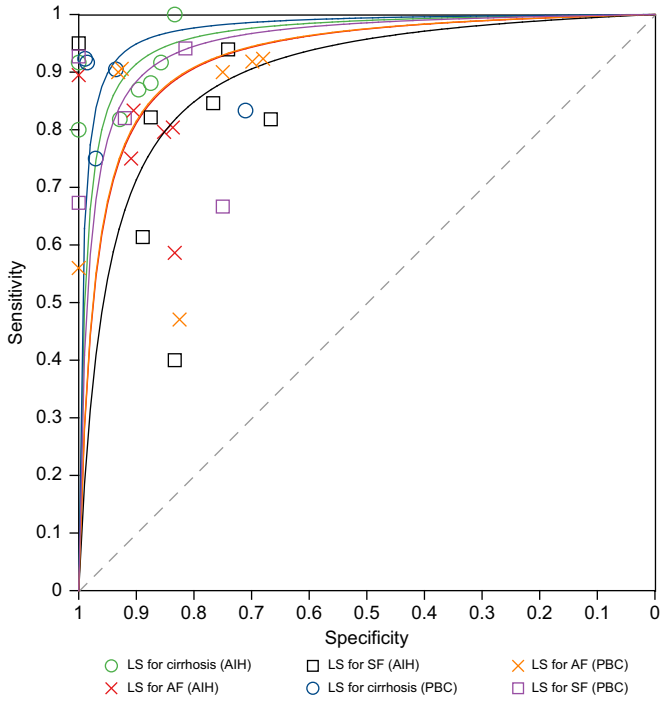

Fig. 1. Summary ROC plot of liver stiffness by transient elastography in detecting significant fibrosis, advanced fibrosis and cirrhosis in individuals with AIH and PBC. The summary sensitivity and specificity were calculated for each enrolled study and the summary ROC plot was produced in Review Manager (Revman 5.3 version). AF, advanced fibrosis; AIH, autoimmune hepatitis; LS, liver stiffness; PBC, primary biliary cholangitis; SF, significant fibrosis.