Title

Editorial: Recent advances in fibrosis assessment for metabolic dysfunction-associated fatty liver disease - authors' reply

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We appreciate the elegant Editorial by Drs Jeffrey and Adams on our recently published study.[1,2] In our study, we found that deep learning-based analyses combined with multi-photon microscopy (MPM) digital pathology accurately identified the histological stages of liver fibrosis in Chinese adults with metabolic dysfunction-associated fatty liver disease (MAFLD).

The traditional processes for obtaining liver histology images that require staining and labelling the images by experienced histopathologists are time-consuming and potentially prone to subjective bias. Artificial intelligence (AI) based digital pathology is becoming a mainstream option for routine diagnostics.[3] Developing an AI-based diagnostic platform for pathologists may potentially overcome these shortcomings.[4] For that reason, we aimed to develop an automated quantitative tool for the visualization of liver tissues, named AutoFibroNet, which is based on MPM images and deep learning analyses and has substantive advantages over traditional methods, including being fast, label-free, and reproducible.

The digital pathology image analysis approach has changed in recent years due to important advances in deep learning analysis for image classification tasks.[4] Some recent studies have found that AI-based analysis using digital pathology could detect earlier changes in different zones of the liver lobule in response to drug treatments, that may not have been detected using conventional microscopy.[5,6] In addition to detecting early drug-induced changes in the liver lobule, AI-based digital pathology

can also predict the development of portal hypertension in patients with MAFLD.[7] This also increases hope for predicting adverse extrahepatic clinical outcomes, including cardiovascular and renal outcomes, strongly associated with MAFLD.[8,9]

As Drs Jeffrey and Adams state in their Editorial, the efficacy of deep learning is influenced by the quality and representativeness of training data. Using deep learning models alone may be sensitive to small changes in image quality, but we usually cannot determine the source of the error.[10] In our study, transfer learning was used to reduce the need for extensive training data sets. We used this method to further improve our deep learning model, thus developing a joint model that integrated deep learning features with manual features.

We agree with Drs Jeffrey and Adams that it remains uncertain if our AutoFibroNet model offers better accuracy for assessing the histological severity of liver fibrosis than other developed automated quantitative models, such as q-FP and qFIBS. The comparison between different automated quantitative histological models requires multicentre studies and co-operation among investigators. Therefore, we call for multicentre and multi-national data sharing, together with global cohort development of diagnostic pathology platforms.[11]

If AI diagnostic platforms could significantly improve diagnostic accuracy and efficiency for patients and hospitals, eliminating these technical barriers (e.g.

implementing a digital pathology platform) may become an expectation for any hospital committed to delivering tertiary health care to patients with MAFLD. Taken together, we believe that deep learning-based MPM imaging holds great promise for becoming the pathology decision support system of the future and the new “gold standard” for the diagnosis and histological assessment of MAFLD.

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References

1. Jeffrey AW, Adams LA. Editorial: Recent advances in fibrosis assessment for metabolic dysfunction associated fatty liver disease. Aliment Pharmacol Ther 2023; in press.
2. Zhan H, Chen S, Gao F, et al. AutoFibroNet: A deep learning and multi-photon microscopy-derived automated network for liver fibrosis quantification in MAFLD. *Aliment Pharmacol Ther.* 2023; in press.
3. Jahn SW, Plass M, Moinfar F. Digital Pathology: Advantages, Limitations and Emerging Perspectives. *Journal of clinical medicine.* 2020;9(11).
4. Campanella G, Hanna MG, Geneslaw L, et al. Clinical-grade computational pathology using weakly supervised deep learning on whole slide images. *Nature medicine.* 2019;25(8):1301-1309.
5. Anstee QM, Lucas KJ, Francque S, et al. Tropifexor plus cenicriviroc combination versus monotherapy in non-alcoholic steatohepatitis: Results from the Phase 2b TANDEM study. *Hepatology (Baltimore, Md).* 2023.
6. Sanyal AJ, Lopez P, Lawitz EJ, et al. Tropifexor for nonalcoholic steatohepatitis: an adaptive, randomized, placebo-controlled phase 2a/b trial. *Nature medicine.* 2023;29(2):392-400.
7. Noureddin M, Goodman Z, Tai D, et al. Machine learning liver histology scores correlate with portal hypertension assessments in nonalcoholic steatohepatitis cirrhosis. *Alimentary pharmacology & therapeutics.* 2023;57(4):409-417.
8. Sun DQ, Targher G, Byrne CD, et al. An international Delphi consensus statement on metabolic dysfunction-associated fatty liver disease and risk of

chronic kidney disease. *Hepatobiliary Surg Nutr.* 2023;12(3):386-403.
9. Zhou XD, Targher G, Byrne CD, et al. An international multidisciplinary consensus statement on MAFLD and the risk of CVD. *Hepatology international.* 2023:1-19.
10. Belthangady C, Royer LA. Applications, promises, and pitfalls of deep learning for fluorescence image reconstruction. *Nature methods.* 2019;16(12):1215-1225.
11. Kang Y, Kim YJ, Park S, et al. Development and operation of a digital platform for sharing pathology image data. *BMC medical informatics and decision making.* 2021;21(1):114.