Editorial Commentary

Practice guidance documents for the diagnosis and management of non-alcoholic fatty liver disease—recent updates and open questions

Volker M. Lauschke[1,2,3]^

[1]Dr Margarete Fischer-Bosch Institute of Clinical Pharmacology, Stuttgart, Germany; [2]Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden; [3]University Tübingen, Tübingen, Germany

Correspondence to: Prof. Volker M. Lauschke, PhD. Dr Margarete Fischer-Bosch Institute of Clinical Pharmacology, Auerbachstr. 112., 70 376 Stuttgart, Germany; Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden; University Tübingen, Tübingen, Germany. Email: volker.lauschke@ikp-stuttgart.de.

Comment on: Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, *et al.* AASLD Practice Guidance on the clinical assessment and management of non-alcoholic fatty liver disease. Hepatology 2023;77:1797-835.

Keywords: Guidelines; non-alcoholic steatohepatitis (NASH); fibrosis; individualized medicine

Submitted Jul 26, 2023. Accepted for publication Aug 20, 2023. Published online Sep 18, 2023.
doi: 10.21037/hbsn-23-376
View this article at: https://dx.doi.org/10.21037/hbsn-23-376

Primarily driven by an increasingly sedentary lifestyle and hypercaloric nutritionally imbalanced diets, non-alcoholic fatty liver disease (NAFLD) has emerged as the most prevalent liver disease in the US and Europe. NAFLD constitutes an umbrella term that includes a spectrum of disease from non-alcoholic fatty liver (NAFL) to non-alcoholic steatohepatitis (NASH), NASH fibrosis and NASH cirrhosis that are all characterized by ≥5% of all hepatocytes being steatotic in patients with little alcohol intake and no apparent alternative causes. The American Association for the Study of Liver Diseases (AASLD) has recently provided an updated comprehensive guidance document that provides 29 actionable statements to improve diagnosis and patient management of adult NAFLD in clinical practice taking into account the recent advances in risk assessment and therapeutic measures (1).

The new document provides an update of the previous AASLD practice guidance from 2018 (2). For patients with incidental findings of hepatic steatosis, AASLD recommends evaluation of metabolic comorbidities, alcohol intake as well as the exclusion of other etiologies, such as genetic disease, nutrient deficiencies or exposure to drugs known to impact hepatic *de novo* lipogenesis or β-oxidation. One important innovation of the update is the algorithm for risk stratification in patients with a clinically suspected or established NAFLD. The main purpose of this evaluation is to exclude advanced fibrosis using a test with high negative predictive value (NPV). To this end, the AASLD recommends the fibrosis 4 (FIB-4) score as a non-invasive blood-based test that exhibited consistently good prognostication in secondary or tertiary care settings across studies (3). These recommendations align well with guidelines from the Asian Pacific Association for the Study of the Liver (APASL) that recommend either non-invasive tests or liver stiffness measurements (LSM) for the exclusion of advanced fibrosis (4). However, correlation of FIB-4 with LSM showed high rates of false negatives up to 46% in patients with multiple risk factors, indicating that the reliance on FIB-4 for specialist referrals might be problematic (5,6). In contrast, the algorithm recommended by the European Association for the Study of the Liver (EASL) additionally suggests referral to gastrointestinal specialist centers for every patient with steatosis and liver enzyme abnormalities, which the AASLD guidance considers unreliable as they are frequently normal in patients with advanced liver disease (7). It remains to be determined, which process provides increased patient benefits.

^ ORCID: 0000-0002-1140-6204.

Table 1 Comparison of important recommendations regarding the NASH diagnosis and management issued by major international societies

Recommendation	AASLD	EASL	APASL
Risk groups recommended for NAFLD screening	Diabetics and patients with complicated obesity, family history of cirrhosis or moderate-to-high alcohol consumption	Diabetics and all individuals with persistently abnormal liver enzymes, obesity or MetS	Diabetics and all individuals who are overweight, obese or have been diagnosed with MetS
Screenings recommended for patients with steatosis	Diabetes	Features of MetS, evaluation of CVD	Features of MetS, evaluation of CVD and cardiovascular risk
Identification of steatosis	Standard ultrasound not recommended to identify hepatic steatosis. Steatosis should be identified using CAP or MRI-PDFF	Ultrasound is recommended as first-line. MRS is the only quantitative method, but not recommended in clinical practice	Ultrasound is recommended as first-line. Alternatives are CAP and transient elastography. MRS and MRI-PDFF not recommended in clinical practice
Identification of NASH	Serum and imaging-based methods not yet fit for routine clinical practice	NASH has to be diagnosed by a liver biopsy	NASH has to be diagnosed by a liver biopsy. Exclusion using elastography or blood biomarkers and scores of fibrosis
Identification of fibrosis	FIB-4 risk assessment recommended. Advanced fibrosis or cirrhosis needs to be confirmed by liver biopsy	NFS, FIB-4, ELF or FibroTest with or without transient elastography. Advanced fibrosis or cirrhosis needs to be confirmed by liver biopsy	NFS, FIB-4, ELF or FibroTest with or without transient elastography. Advanced fibrosis or cirrhosis needs to be confirmed by liver biopsy
Dietary & lifestyle recommendations	Hypocaloric diet & increased physical activity; abstinence from alcohol in NASH fibrosis	Hypocaloric diet free of processed food, as well as food and beverages high in added fructose. Increased physical activity	
Endorsements of pharmacological treatments for NASH	Semaglutide (for patients with T2DM/obesity), pioglitazone (for patients with T2DM) or vitamin E	Pioglitazone (also off-label) or vitamin E	No firm recommendations
Bariatric surgery	Useful measure to improve the histological lesions of NAFLD. Decompensated cirrhosis is absolute exclusion criterion	Useful measure to improve the histological lesions of NAFLD. No recommendation regarding the use in cirrhosis	Useful measure to improve the histological lesions of NAFLD. Individualized decision in cirrhotic patients
Therapeutic measures for dyslipidemia	Statins, omega-3 FAs, icosapent ethyl or fibrates	Statins, omega-3 FAs	Statins should be considered in all patients with NAFLD and hyperlipidemia
Follow-up	Low risk patients with steatosis: every 2–3 years; in patients with prediabetes, T2DM or 2 or more metabolic risk factors: 1–2 years; patients with biopsy confirmed fibrosis: annually	NAFL patients without worsening of metabolic risk factors: 2–3-years; patients with NASH and/or fibrosis: annually; patients with NASH cirrhosis: every 6 months; if indicated on a case-by-case basis, liver biopsy could be repeated after 5 years	

NASH, non-alcoholic steatohepatitis; AASLD, American Association for the Study of Liver Diseases; EASL, European Association for the Study of the Liver; APASL, Asian Pacific Association for the Study of the Liver; NAFLD, non-alcoholic fatty liver disease; MetS, metabolic syndrome; CVD, cardiovascular disease; CAP, controlled attenuation parameter; MRI-PDFF, magnetic resonance imaging–proton density fat fraction; MRS, magnetic resonance spectroscopy; FIB-4, fibrosis 4 calculator; NFS, NAFLD fibrosis score; ELF, enhanced liver fibrosis; T2DM, type 2 diabetes mellitus; FA, fatty acid.

While guidance by the different major societies aligns overall well, some further notable differences remain, particularly with regards to diagnostic modalities (*Table 1*). One major difference is the negative recommendation regarding the use of ultrasound for the detection of steatosis. The AASLD guidance recommends magnetic resonance imaging–proton density fat fraction (MRI-PDFF) and elastography with controlled attenuation parameter (CAP) as methods of choice for the identification of steatosis whereas the use of ultrasound is explicitly not recommended due to its low sensitivity. In contrast, ultrasound is the preferred first-line diagnostic procedure for imaging of NAFLD both EASL and APASL, whereas MRI is not recommended for routine clinical practice due to its high cost, despite being recognized as the gold standard to quantify liver fat. Furthermore, for large-scale studies EASL and APASL endorse the use of serum biomarkers, such as the fatty liver index (FLI), NAFLD liver fat score (NAFLD-LFS), hepatic steatosis index (HSI), visceral adiposity index (VAI) and triglyceride-glucose (TyG) index, which can predict the presence, but not the severity, of steatosis with acceptable accuracy [positive predictive values (PPVs) of 99% and NPVs of 10–16%] (8).

Which points remain to be addressed?

The current guidance document focusses on adult NAFLD, whereas similar updated AASLD recommendations for the diagnosis and management of NASH in children and juveniles are currently lacking. The author refers to a separate upcoming guidance document for these patient groups, which is urgently needed.

(I) There is furthermore ongoing discussion about the nomenclature of fatty liver disease. The APASL has abandoned the acronym NAFLD for the overarching term "metabolic (dysfunction) associated fatty liver disease (MAFLD)" that better reflects disease pathogenesis (9). While this change might help in the identification and recognition of disease subtypes, it would arguably be beneficial for both patients and clinicians if terminology could be standardized between the different societies and expert groups as soon as possible.

(II) Genetic variants in multiple risk genes have been consistently associated with NAFLD onset and progression (10). Most pronounced are the effects of variations in *PNPLA3*, *TM6SF2*, *GCKR*, *MBOAT7* and *HSD17B13* with moderate-to-large effect sizes. However, their inclusion into personalized risk stratification algorithms is currently not recommended in clinical practice by either AASLD or APASL. The European guidance does not endorse routine genetic testing for these variations either but recommends consideration of genotyping in selected patients and clinical studies. With increasing prevalence of medical genomics and direct-to-consumer genetic testing, more and more individuals with incident NAFLD diagnoses will have information about their genetic risk factors. Consequently, ongoing discussions about if and how such information can be included into individualized risk assessments are required, particularly in light of emerging prospective evidence indicating that integration of clinical fibrosis markers with polygenic risk scores can refine prediction of NAFLD, NASH fibrosis and hepatocellular carcinoma (11,12). Besides genetic factors, recent proteomic investigations revealed that plasma protein signatures can discriminate between NAFLD and NASH cirrhosis (13). Combined, these results exemplify the rapid development in NASH biomarker identification some of which will likely transpire into clinical guidance in the near future.

(III) The new AASLD guidance emphasizes the need to manage common medical comorbidities, such as type 2 diabetes, hypertension and obesity with a prioritization of medicines that also might have benefits for NASH. These include pioglitazone for patients with diabetes, semaglutide for diabetes and obesity, vitamin E in patients without diabetes, as well as the use of statins, omega-3 fatty acids, icosapent ethyl or fibrates for the management of dyslipidemias. Multiple drugs are currently in late clinical stages of development. Arguably the most promising current candidates to be the first approved drug for NASH are the THRβ agonist resmetirom and the pan-PPAR agonist lanifibranor, which both show significant improvement with regards to NASH resolution and decrease in fibrosis (14). Based on these data it appears reasonable to assume that regulatory approvals of drugs for the treatment of NASH within the next 3–5 years are likely. Once available, NASH-specific pharmacotherapy can be expected to result in major impacts on patient management and clinical guidance. In these developments it will be imperative to maintain a patient-centric

focus that considers inter-individual differences in demographic factors, disease phenotypes and comorbidities. The current guideline's strong emphasis on the multidisciplinarity of NAFLD patient care provides an excellent basis to integrate such developments with lifestyle and dietary measures in the future.

Acknowledgments

Funding: The work in the author's laboratory is funded by the Swedish Research Council (Nos. 2019-01837 and 2021-02801), by the EU/EFPIA/OICR/McGill/KTH/Diamond Innovative Medicines Initiative 2 Joint Undertaking (EUbOPEN No. 875510) and by the Robert Bosch Stiftung, Stuttgart, Germany.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Hepatobiliary Surgery and Nutrition*. The article did not undergo external peer review.

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-376/coif). VML is CEO and shareholder of HepaPredict AB.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, et al. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology 2023;77:1797-835.
2. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2018;67:328-57.
3. Lee J, Vali Y, Boursier J, et al. Prognostic accuracy of FIB-4, NAFLD fibrosis score and APRI for NAFLD-related events: A systematic review. Liver Int 2021;41:261-70.
4. Eslam M, Sarin SK, Wong VW, et al. The Asian Pacific Association for the Study of the Liver clinical practice guidelines for the diagnosis and management of metabolic associated fatty liver disease. Hepatol Int 2020;14:889-919.
5. Viganò M, Pugliese N, Cerini F, et al. Accuracy of FIB-4 to Detect Elevated Liver Stiffness Measurements in Patients with Non-Alcoholic Fatty Liver Disease: A Cross-Sectional Study in Referral Centers. Int J Mol Sci 2022;23:12489.
6. Graupera I, Thiele M, Serra-Burriel M, et al. Low Accuracy of FIB-4 and NAFLD Fibrosis Scores for Screening for Liver Fibrosis in the Population. Clin Gastroenterol Hepatol 2022;20:2567-76.e6.
7. European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol 2016;64:1388-402.
8. Fedchuk L, Nascimbeni F, Pais R, et al. Performance and limitations of steatosis biomarkers in patients with nonalcoholic fatty liver disease. Aliment Pharmacol Ther 2014;40:1209-22.
9. Eslam M, Sanyal AJ, George J, et al. MAFLD: A Consensus-Driven Proposed Nomenclature for Metabolic Associated Fatty Liver Disease. Gastroenterology 2020;158:1999-2014.e1.
10. Carlsson B, Lindén D, Brolén G, et al. Review article: the emerging role of genetics in precision medicine for patients with non-alcoholic steatohepatitis. Aliment Pharmacol Ther 2020;51:1305-20.
11. De Vincentis A, Tavaglione F, Jamialahmadi O, et al. A Polygenic Risk Score to Refine Risk Stratification and Prediction for Severe Liver Disease by Clinical Fibrosis Scores. Clin Gastroenterol Hepatol 2022;20:658-73.
12. Bianco C, Jamialahmadi O, Pelusi S, et al. Non-invasive

stratification of hepatocellular carcinoma risk in non-alcoholic fatty liver using polygenic risk scores. J Hepatol 2021;74:775-82.
13. Sveinbjornsson G, Ulfarsson MO, Thorolfsdottir RB, et al. Multiomics study of nonalcoholic fatty liver disease. Nat Genet 2022;54:1652-63.
14. Harrison SA, Loomba R, Dubourg J, et al. Clinical Trial Landscape in NASH. Clin Gastroenterol Hepatol 2023;21:2001-14.

Cite this article as: Lauschke VM. Practice guidance documents for the diagnosis and management of non-alcoholic fatty liver disease—recent updates and open questions. HepatoBiliary Surg Nutr 2023;12(5):780-784. doi: 10.21037/hbsn-23-376