



Opportunistic case-finding of liver fibrosis in metabolic dysfunction-associated steatotic liver disease (MASLD) by leveraging integrated care pathways of type 2 diabetes

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Comment on: Lindfors A, Strandberg R, Hagström H. Screening for advanced liver fibrosis due to metabolic dysfunction-associated steatotic liver disease alongside retina scanning in people with type 2 diabetes: a cross-sectional study. *Lancet Gastroenterol Hepatol* 2025;10:125-37.

Keywords: Metabolic dysfunction-associated steatotic liver disease (MASLD); steatotic liver disease; screening; type 2 diabetes (T2D); retinopathy

Submitted May 18, 2025. Accepted for publication Aug 06, 2025. Published online Sep 26, 2025.

doi: 10.21037/hbsn-2025-324

View this article at: <https://dx.doi.org/10.21037/hbsn-2025-324>

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a global health burden that requires early screening, diagnosis, and intervention

MASLD is a leading cause of chronic liver disease globally, with an estimated prevalence of 38% worldwide (1,2). MASLD is the new term that replaces what was previously known as non-alcoholic fatty liver disease (NAFLD). Rather than a single clinical entity, MASLD represents a heterogeneous disease continuum, encompassing a range of hepatic conditions, from isolated steatosis to metabolic dysfunction-associated steatohepatitis (MASH), progressive fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). MASLD is a major cause of liver cirrhosis, an end-stage liver disease, and is associated with high morbidity and mortality, and may eventually lead to liver transplantation (3).

The screening process is pivotal for the early detection

and diagnosis of MASLD. While the disease often follows a clinically silent course for many years, it may remain unrecognized unless actively sought, especially in at-risk populations. For this reason, it is essential that healthcare professionals maintain a high level of awareness to facilitate timely diagnosis and intervention. The backbone of therapy largely consists of lifestyle and management of metabolic comorbidities (4). Importantly, resmetirom is currently the only pharmacological treatment approved for MASH, and its approval is, for now, limited to the United States (5). Resmetirom's Food and Drug Administration (FDA) approval highlights the critical role of non-invasive tests (NITs) for MASH management. While current NITs like fibrosis-4 index (FIB-4) and vibration-controlled transient elastography (VCTE) have shown limitations in accuracy, reliability, and widespread applicability, they present immense potential. Rigorous validation, technological advancements, and the establishment of standardized non-invasive assessment

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Table 1 Summary of the key recommendations from European and American guidelines on MASLD screening and referral pathways

Recommendations	EASL-EASD-EASO (Europe)	AASLD (US)
Preferred methods	First line: serum-based scores (e.g., FIB-4 [†]) Confirmatory tests: imaging techniques (e.g., VCTE, MRE), serum-based fibrosis tests (e.g., ELF and FibroTest), liver biopsy	First line: FIB-4 Confirmatory tests: imaging techniques (e.g., VCTE, MRE), serum-based fibrosis tests (e.g., ELF), liver biopsy
Screened population	Patients with one of the following: T2D; abdominal obesity + at least one metabolic risk factor [‡] ; persistent elevation in liver enzymes; incidentally discovered steatosis on imaging	Patients with one of the following: T2D; obesity + metabolic risk factor; first-degree relative of a patient with cirrhosis due to NAFLD/MASH; moderate alcohol consumption; incidentally discovered steatosis on imaging, pre-diabetes, or ≥2 metabolic risk factors
Low-risk [§]	Repeat every 1–3 years	Repeat FIB-4 test every 1–2 years: if type 2 diabetic or prediabetic, or having at least two metabolic risk factors Repeat FIB-4 test every 2–3 years if no T2D and <2 metabolic risk factors
Intermediate risk [§]	Two pathways are proposed: (I) Risk stratification based on VCTE, ELF, MRE or SWE: (i) VCTE <8 kPa—same as (II); (ii) VCTE ≥8 kPa—refer to hepatologist (II) Management of risk factors [¶] then reassessment after ≤1 year: (i) FIB-4 <1.3: repeat every 1–3 years; (ii) FIB-4 ≥1.3: risk stratification using the above confirmatory imaging methods	Risk stratification based on VCTE or ELF: (I) VCTE <8 kPa or ELF <7.7: reassess as above in low-risk population (II) VCTE ≥8 kPa or ELF ≥7.7 or persistent elevated AST and/or ALT for >6 months: hepatologist/gastroenterologist referral
High risk [§]	Refer to hepatologist	Refer to hepatologist/gastroenterologist

[†], FIB-4 is not accurate in patients <35 years (17). AASLD recommends using NITs (e.g., VCTE or ELF) in patients <35 years with metabolic comorbidities or elevated transferases. FIB-4 = (age × AST)/(platelets × √ALT). [‡], metabolic risk factors are obesity, increased waist circumference, type 2 diabetes, dyslipidemia, and hypertension. [§], low risk: FIB-4 <1.3 in patients ≤65 years (in patients >65 years, the cutoff is <2); intermediate risk: FIB-4: 1.3–2.67 in patients ≤65 years (in patients >65 years, the cutoff is 2–2.67); high risk: FIB-4 >2.67. [¶], both scientific societies recommend lifestyle modification, optimizing treatment for underlying conditions, ongoing alcohol assessment, using MASLD medications, and the use of bariatric surgery in selected patients. AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; AST, aspartate aminotransferase; EASD, European Association for the Study of Diabetes; EASL, European Association for the Study of the Liver; EASO, European Association for the Study of Obesity; ELF, enhanced liver fibrosis; FIB-4, fibrosis-4 index; MASLD, metabolic dysfunction-associated steatotic liver disease; MRE, magnetic resonance elastography; NAFLD, non-alcoholic fatty liver disease; MASH, metabolic dysfunction-associated steatohepatitis; NITs, non-invasive tests; SWE, shear wave elastography; T2D, type 2 diabetes; VCTE, vibration-controlled transient elastography.

protocols are crucial to improve their precision and overcome operational challenges. These improvements are essential for NITs to become a reliable and generalizable tool for resmetirom indication and monitoring across diverse patient populations. Such advancements will optimize MASH patient management and drug efficacy.

Current recommendations for fibrosis-focused screening for MASLD patients and targeted screening in diabetic patients

As liver fibrosis is the most relevant driver of disease

progression and clinical events, MASLD screening and referral pathways strongly rely on assessment of the risk of fibrosis by means of NITs. These are divided into three main categories: serologic, imaging NITs and the combination of both (6). There is a growing global consensus supporting screening for hepatic fibrosis in populations at risk for MASLD (7). Both the 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) and American Association for the Study of Liver Diseases (AASLD) guidelines offer similar recommendations on how to screen

these populations (Table 1) (8,9). These scientific societies agree on the categorization of patients into three risk groups, low, intermediate, and high, with corresponding management strategies. Both guidelines emphasize the need for a second noninvasive evaluation in individuals at intermediate risk in order to appropriately classify fibrosis risk. The more thoroughly studied high-risk population for MASLD/MASH and fibrosis as of today is patients with type 2 diabetes (T2D), who present high rates of both steatohepatitis and fibrosis and a more rapid course of disease progression (10). This has led experts to propose that patients with T2D require specific screening pathways for MASLD and more comprehensive appraisals of liver health in general (11).

Lindfors *et al.* (12) proposed a novel approach for screening diabetic patients for MASLD by performing VCTE during routine retinal screening visits at an outpatient ophthalmology clinic. In this study, 1,005 patients were screened, and complete measurements were obtained for 973 individuals. The prevalence of MASLD was estimated at 51.8% (504/977). Of the total screened population, 15.8% (154/977) had liver stiffness measurements (LSM) ≥ 8.0 kPa, suggestive of liver fibrosis, and 5.0% (49/977) had LSM >12.0 kPa, indicative of advanced fibrosis. A secondary assessment was performed in patients with elevated or unreliable initial results. Among these, 45.2% (56/124) had follow-up LSMs <8.0 kPa, suggesting false-positive results, while 54.8% (68/124) maintained elevated values. In total, 7.4% (74/1,005) of the cohort had confirmed LSMs ≥ 8.0 kPa, suggesting significant fibrosis, and 2.9% (29/1,005) had values >12.0 kPa, suggestive of advanced fibrosis. Factors associated with elevated liver stiffness values were high body mass index (BMI), increased controlled attenuation parameter (CAP) values, and the presence of severe diabetic retinopathy.

LSM has demonstrated progressively improved diagnostic performance with advancing stages of liver fibrosis. For instance, reported sensitivities are approximately around 83%, 94%, 92%, and 95%, and specificities of 88%, 89%, 70%, and 71% for detecting fibrosis stages $\geq F1$, $\geq F2$, $\geq F3$, and $F4$, respectively. Similarly, in patients with MASLD, sensitivity of 93.7% and specificity of 91.1% for $\geq F3$ [negative predictive value (NPV) 95.9%], and 96.2%/92.2% for $F4$ (NPV 98.5%) were described (13). Overall, the area under the receiver operating characteristic curve (AUROC) values for advanced fibrosis ($\geq F3-4$) frequently exceed 0.80, indicating high diagnostic accuracy. Consequently, VCTE achieves particularly high negative predictive values for

ruling out advanced liver damage. However, its ability to discriminate between early stages (e.g., $F0$ vs. $F1$) remains limited due to overlapping liver stiffness values among these groups.

MASLD screening in primary care services, limitations of the FIB-4 screening test, and gaps in follow-up

Given the central role of primary care systems in screening and managing chronic diseases, it is essential to explore new approaches that facilitate screening populations at risk for MASLD in this setting. European and American guidelines recommend the use of the FIB-4 score to screen for MASLD in primary care (8,9). However, FIB-4 has some limitations that might hinder generalizability, like unreliable results in patients <35 years old and patients with elevated transaminases or metabolic abnormalities (9).

Another key limitation is the wide intermediate risk range (FIB-4 between 1.3–2.67 for individuals ≤ 65 years, and 2.0–2.67 for those >65 years), which often necessitates a second assessment with imaging or serum-based NITs. A retrospective cohort study (14), including 52,006 patients, assessed the use of FIB-4 for MASLD screening in primary care and found that 23% of patients were classified as intermediate to high, requiring further assessment via specialist referral or VCTE. Despite this, only 10% of those at risk completed the second-line evaluation.

These challenges appear even more pronounced when screening individuals with T2D in the primary care system. Boursier *et al.* found that almost a third of patients with T2D with normal FIB-4 as the first step of the screening pathway were subsequently found to have advanced fibrosis by liver biopsy (15). This further underscores the relevance of the study by Lindfors *et al.*, which demonstrated a high acceptance rate (77%) for opportunistic VCTE screening in ophthalmology clinics (12).

VCTE-based screening: balancing precision and feasibility

Notably, Lindfors *et al.* reported a high rate of false positives for suspected significant liver fibrosis in the initial VCTE assessment, with nearly half of the patients not having fibrosis confirmed on the second evaluation (12). This finding is consistent with previous studies, which have also highlighted several factors that can influence VCTE accuracy. These include operator experience, probe

type (e.g., M vs. XL), lack of fasting or recent alcohol consumption, and patient-related factors such as obesity, ascites, hepatitis, or heart failure, all of which can reduce measurement reliability (6).

Additionally, the authors acknowledge that, for this screening approach to be broadly applicable, it would require the availability of centralized retinal centers equipped to offer both ophthalmologic and hepatologic services, a condition that may not be feasible in resource-limited healthcare systems. However, a notable strength of VCTE is its versatility: it can be performed not only by specialists but also by trained non-specialist healthcare providers, such as nurses or general practitioners, which may help broaden access to fibrosis screening (16).

Conclusions

In summary, the study by Lindfors *et al.* nicely illustrates that systematic case-finding for liver fibrosis in MASLD amongst high-risk populations is feasible and leads to the detection of at-risk patients. Whether this can be successfully implemented in most settings and its cost-effectiveness and cost-equity remain to be determined. Embedding VCTE into retinopathy screening visits in people with T2D paves the way for future centralized opportunistic approaches for MASLD case-finding and highlights the need for more accurate and reliable testing strategies. Future studies should explore whether incorporating alternative serological NITs or refining existing cutoffs could help reduce false-positive rates and improve overall diagnostic performance.

Acknowledgments

None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *HepatoBiliary Surgery and Nutrition*. The article has undergone external peer review.

Peer Review File: Available at <https://hbsn.amegroups.com/article/view/10.21037/hbsn-2025-324/prf>

Funding: None.

Conflicts of Interest: All authors have completed the ICMJE

uniform disclosure form (available at <https://hbsn.amegroups.com/article/view/10.21037/hbsn-2025-324/coif>). J.M.P. reports grants from EC/EFPIA, European Commission, Instituto de Salud Carlos III, and Next Generation EUSCIII/IBEC Barcelona City Council-“La Caixa” Foundation; consulting fees from Boehringer-Ingelheim, Novo Nordisk, and Madrigal; honoraria from Madrigal, Novo Nordisk, and Boehringer-Ingelheim; support for attending meetings from Boehringer-Ingelheim, Madrigal, and Novo Nordisk. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are 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.

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Cite this article as: Makary A, Rojo D, Pagès L, Sabiote C, Jiménez-Masip A, Pericàs JM. Opportunistic case-finding of liver fibrosis in metabolic dysfunction-associated steatotic liver disease (MASLD) by leveraging integrated care pathways of type 2 diabetes. *HepatoBiliary Surg Nutr* 2025;14(5):824-828. doi: 10.21037/hbsn-2025-324