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Nasirdinov Murodjon Adahamjon o`g`li

Assistant, Department of Family Physician Training

Andijan State Medical Institute

Uzbekiston, Andijon

MODERN APPROACHES, ALGORITHMS, AND PRACTICAL RECOMMENDATIONS FOR EARLY DETECTION OF METABOLIC DYSFUNCTION–ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)

Abstract

Metabolic dysfunction–associated steatotic liver disease (MASLD; formerly NAFLD) affects a significant share of the population and is closely linked to cardiometabolic risk factors such as type 2 diabetes, obesity, and dyslipidemia. Early diagnosis is particularly important in the spectrum of liver diseases because the key prognostic determinant—fibrosis stage—often remains clinically silent for a long time. In recent years, clinical guidelines have proposed a two-step strategy (initial triage + confirmation): first, simple serum-based scores such as FIB-4/NFS to identify a "low-risk" group, followed in "intermediate/high-risk" patients by noninvasive imaging and elastographic methods (VCTE/FibroScan, 2D-SWE, MRE) for early detection of fibrosis. For quantitative assessment of steatosis, MRI-PDFF is considered the reference method; the Controlled Attenuation Parameter (CAP, on FibroScan) and newer ultrasound attenuation metrics are increasingly used in practice. For fibrosis risk prediction, the ELF test (HA, PIIINP, TIMP-1) is widely applied; fibrogenesis markers such as PRO-C3 are also promising. This review systematizes current terminology (MASLD/MASH), identifies target groups for screening, provides practical cut-offs, outlines strengths and limitations of key tools, and proposes a simplified, practice-oriented algorithm adapted to the healthcare context of Uzbekistan. (Sources: AASLD 2023 guidance; EASL-EASD-EASO 2024 guidelines; meta-analyses and large studies.) (PubMed)

Key words: MASLD (NAFLD), MASH (NASH), early diagnosis, FIB-4, NFS, VCTE/FibroScan, CAP, MRI-PDFF, MRE, ELF, PRO-C3.

1. Terminology and why "early" matters

1.1. Renaming NAFLD → MASLD

In 2023, leading professional societies proposed replacing “NAFLD” with “MASLD” (metabolic dysfunction–associated steatotic liver disease). This change not only reduces the stigma implied by the term “non-alcoholic” but also more accurately reflects disease biology by placing metabolic dysfunction at the center of pathogenesis. Under the umbrella term SLD (steatotic liver disease), different causes of steatosis are grouped, while the inflammatory phenotype is now termed MASH (metabolic dysfunction–associated steatohepatitis). Diagnostic criteria were also refined: to establish the diagnosis, evidence of hepatic steatosis must be combined with at least one cardiometabolic risk factor. (journal-of-hepatology.eu)

1.2. Why detect early?

Long-term outcomes in steatotic liver disease are determined primarily by the stage of fibrosis. At early stages (F0–F2), changes are potentially reversible: lifestyle modification and strict control of metabolic risk can reduce progression and sometimes induce regression. By contrast, stages F3–F4 are associated with higher risks of decompensated cirrhosis, hepatocellular carcinoma (HCC), and liver transplantation. Therefore, modern practice emphasizes “fibrosis-oriented” screening in which the primary goal is to identify, as early as possible, patients likely to harbor advanced fibrosis. (journals.lww.com)

2. Who should be prioritized for screening?

European (EASL–EASD–EASO, 2024) and American (AASLD, 2023) guidelines agree that active case-finding is warranted among high-risk groups. These include patients with type 2 diabetes, obesity (especially BMI ≥30 and central adiposity), atherogenic dyslipidemia and other components of the metabolic syndrome, as well as individuals with persistently abnormal ALT/AST or incidentally detected steatosis on imaging. For adults over 65, score cut-offs should be recalibrated to account for age-related features. (PMC) **Practical takeaway for Uzbekistan:** at the primary care level (family physician/endocrinologist), targeted assessment of liver risk should be considered standard quality care for every patient with type 2 diabetes or obesity.

3. Primary laboratory stratification: simple scoring systems

3.1. FIB-4 (Fibrosis-4)

FIB-4 is the most validated rule-out tool and helps safely exclude advanced fibrosis in many patients. In those aged 35–65 years, values <1.3 indicate a low probability of advanced fibrosis (high negative predictive value), whereas values ≥2.67 increase the likelihood of advanced fibrosis (rule-in). In

adults ≥65 years, the lower cut-off is raised to about 2.0 to reduce false positives. The indeterminate zone 1.3–2.67 requires further testing. (aasld.org)

3.2. NAFLD Fibrosis Score (NFS)

Classic NFS cut-offs remain useful: <−1.455 supports exclusion of fibrosis, whereas >0.676 suggests advanced fibrosis. In older adults, false positives are more common, so interpretation should be cautious and context-aware. (PMC)

3.3. APRI and other simple indices

AST/ALT-based indices, including APRI, can be used, but in MASLD they usually perform worse than FIB-4 and NFS. Consequently, most algorithms retain FIB-4 as the first-line test. (aasld.org)

Strengths of this approach: low cost, ready availability from standard chemistry panels, and the ability to quickly identify a low-risk group. **Limitations:** age-dependent threshold shifts, influence of comorbidities (e.g., thrombocytopenia), and a relatively broad "gray zone" requiring additional evaluation.

4. Early detection of fibrosis using noninvasive biomarkers

4.1. ELF (Enhanced Liver Fibrosis)

ELF is a certified test combining hyaluronic acid (HA), PIIINP, and TIMP-1. Lower values (<9.8) are associated with a lower 10-year risk of liver-related outcomes, while higher values (≥11.3) indicate higher risk. When combined with FIB-4, ELF enhances both rule-out and rule-in performance. Regulatory documents specify pre-analytical requirements (e.g., potential effects of biotin, hemolysis). (PMC)

4.2. PRO-C3 and composite panels (FIBC3, ADAPT, ABC3D)

PRO-C3 is a neoepitope of collagen III reflecting active fibrogenesis. Large studies show its utility for detecting advanced fibrosis; it performs best as part of multi-marker panels, which improves robustness and prognostic value. For now, widespread routine use of PRO-C3 lags behind ELF. (PMC)

4.3. Cytokeratin-18 (M30/M65)

CK-18 fragments have been investigated as apoptosis markers in MASH; however, as standalone screening tests they lack sufficient accuracy. They may be useful within expanded multi-marker panels. (PLOS)

Practical summary: in resource-limited settings, the "FIB-4 → VCTE" pathway provides reliable early stratification; when available, ELF and/or PRO-C3 increase informativeness in the indeterminate group.

5. Early detection of steatosis: imaging modalities

5.1. Conventional ultrasound (B-mode)

Meta-analyses show good sensitivity and specificity for moderate-to-severe steatosis (~85%/85%), but sensitivity declines markedly in mild steatosis and results are operator-dependent. Thus, ultrasound is convenient for screening-stage "present/absent" assessment but not for precise quantitative monitoring. (PMC)

5.2. CAP (Controlled Attenuation Parameter, FibroScan)

CAP is broadly comparable to MRI-PDFF in identifying steatosis: pooled data suggest working ranges such as <~249 dB/m to exclude and >~328 dB/m to confirm steatosis, while accounting for device and population specifics. (PMC)

5.3. MRI-PDFF — the quantitative "gold standard"

MRI-PDFF quantifies hepatic fat fraction; in practice, a threshold around 5–6% PDFF is frequently interpreted as indicating steatosis. Research reports provide refined levels aligning with histology (e.g., 5.75%, 15.5%, 21.35%). Clinically, MRI-PDFF is invaluable for accurate therapy monitoring and in drug trials. (kjronline.org)

6. Elastography as the backbone of early noninvasive fibrosis detection

6.1. VCTE (FibroScan) and working cut-offs

Liver stiffness measurement (LSM) by VCTE rapidly stratifies risk. Many sources pragmatically denote zones: <~8 kPa (low risk), 8–12 kPa (intermediate), >~12 kPa (high), acknowledging that exact cut-offs vary by population and clinical context. A 2024 meta-analysis for NAFLD/MASLD indicates 7.1–7.9 kPa as an optimal range for advanced fibrosis detection. (PubMed)

6.2. Magnetic resonance elastography (MRE)

MRE offers higher diagnostic accuracy and helps resolve gray-zone cases, providing slice-by-slice liver maps. Limitations include cost and availability. Many studies discuss thresholds around ~3.6–3.9 kPa for F3. (PMC)

Practical algorithm: if FIB-4 is indeterminate or elevated, perform VCTE; if results are doubtful or discordant with clinical context, add MRE; consider biopsy when the clinical decision is pivotal or discrepancies persist.

7. Advanced MR metrics: cT1 and others

Iron-corrected T1 (cT1) is being explored as a composite marker of inflammation and fibrosis with prognostic value and sensitivity to treatment response. Nevertheless, most guidelines do not yet consider it a routine standard test. (PMC)

8. Genetics and "omics": early-risk stratification

Variants such as PNPLA3 (I148M), TM6SF2, and MBOAT7 may increase the likelihood of fibrosis progression; however, broad genotyping is not recommended for primary screening. In practice, decisions rely mainly on phenotypic risk and clinical context, with simple laboratory and elastographic tools remaining central.

9. Children, women, and other special populations

In pediatrics, ultrasound remains the first step, while VCTE/SWE are gaining ground; MRI-PDFF is appropriate for complex cases and research. During pregnancy, indices should be interpreted with caution and invasive procedures avoided unless essential. In adults ≥65 years, the lower FIB-4 threshold is reasonably raised. (journal-of-hepatology.eu)

10. A simplified "primary care → specialist" algorithm

A stepwise scheme aligned with guidelines is practical in real-world settings. **Step 1 (family physician/endocrinologist):** if T2D, obesity, metabolic syndrome, atherogenic dyslipidemia, persistent ALT/AST abnormalities, or incidental steatosis are present, calculate FIB-4. If <1.3 (or <2.0 in ≥65 years), advanced fibrosis is unlikely: implement lifestyle change, strict cardiometabolic control, and reassessment in 1–2 years. If 1.3–2.67 (or 2.0–2.67 in ≥65 years), proceed to VCTE and/or ELF. If ≥2.67, refer to a specialist center for VCTE ± MRE and consider biopsy. **Step 2 (specialist care):** interpret LSM with population-appropriate cut-offs; stage steatosis by CAP or MRI-PDFF; add ELF for prognostic layering; use MRE to resolve discordance. (PMC; aasld.org; PubMed)

For quantitative steatosis monitoring, MRI-PDFF remains the reference; ultrasound is a practical screening tool; CAP is a convenient quantitative alternative for everyday practice. (ScienceDirect)

11. New horizons: AI and automated ultrasound analysis

Deep-learning approaches to liver ultrasound show encouraging performance in detecting steatosis and possible MASH, with potential to shorten screening times and reduce operator dependence. These technologies are currently mainly in the research phase, but their clinical potential is high. (PMC)

12. Practical "packages" for Uzbekistan

Minimal package (limited resources): routine FIB-4 calculation in patients with T2D/obesity; if FIB-4 ≥1.3, arrange FibroScan (VCTE + CAP) at regional centers; if FIB-4 <1.3, implement lifestyle intervention and reassess in 12–24 months.
Optimal package: FIB-4 → VCTE/CAP; in gray-zone or conflicting cases, add ELF and, if needed, MRE; use MRI-PDFF for clinical trials, complex cases, and precise response monitoring.

13. Brief clinical scenarios

A 52-year-old with T2D and BMI 32: FIB-4 ≈1.1 indicates low risk; recommend lifestyle modification, glycemic and lipid control, and reassessment in 12 months. (aasld.org)
A 60-year-old with severe obesity and T2D: FIB-4 ≈1.6 — VCTE/CAP is required; if LSM is ~9.5 kPa, add ELF or MRE and, once rule-in/rule-out confidence is adequate, decide on biopsy. (PubMed)
A 67-year-old with hypertension and T2D: FIB-4 2.4 (considering ≥2.0 as the lower cut-off for ≥65 years) — expedited VCTE ± ELF; if LSM >12 kPa, plan specialist management and HCC surveillance. (journal-of-hepatology.eu)

14. Strengths and limitations — concise recap

FIB-4/NFS: accessible tools with high NPV, but sensitive to age and comorbidity. ELF: strong prognostic marker but requires laboratory infrastructure. PRO-C3 and composite panels are promising yet still diffusing. Ultrasound is widely available and effective in moderate-to-severe steatosis but limited in mild cases. CAP is a practical quantitative tool with population-dependent cut-offs. MRI-PDFF is a quantitative reference but costly. VCTE is

fast and portable with variable thresholds; MRE provides the highest accuracy but limited access. (PMC; PubMed; kjronline.org)

15. The “step-up” algorithm — in one paragraph

Start by identifying risk groups (T2D, obesity, metabolic syndrome, persistent ALT/AST abnormalities, or ultrasound-detected steatosis) and calculating FIB-4. A value <1.3 (or <2.0 in ≥65 years) classifies the patient as low risk, prompting immediate lifestyle optimization and reassessment in 12–24 months. Values 1.3–2.67 (or 2.0–2.67 in ≥65 years) call for VCTE/ELF. A threshold ≥2.67 warrants referral to specialist care, where VCTE (±CAP) is interpreted, ELF and MRE are added as needed, and biopsy is considered. This stepwise approach reduces burden on tertiary services and improves decision accuracy. (aasld.org; PMC; PubMed)

16. Frequently asked questions and common pitfalls

Normal ALT does **not** exclude MASLD/MASH or advanced fibrosis: screening decisions are phenotype-driven, primarily by the presence of T2D and obesity. (PMC) A normal ultrasound does **not** guarantee absence of disease, since mild steatosis and moderate fibrosis can be missed; FIB-4 and VCTE are required for fibrosis stratification. (CGH Journal) No single test is sufficient: the strategy relies on a sequence in which methods complement each other. (PMC)

17. Conclusion

Early MASLD diagnosis should be two-step, fibrosis-focused, and adapted to healthcare resources. In primary care, FIB-4 functions as a high-NPV “sieve”; at the specialist level, VCTE (±CAP), ELF/MRE as needed, and quantitative steatosis assessment (MRI-PDFF) increase diagnostic confidence and help timely identify high-risk patients. In Uzbekistan, a pragmatic pathway is FIB-4 → VCTE/ELF → MRE/biopsy (as indicated) alongside aggressive management of cardiometabolic risk factors.

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