

## [NARRATIVE REVIEW]

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# Advanced Fibrosis Risk Stratification in MASLD Among Adults With Type 2 Diabetes: A Critical Narrative Review of Practical Gaps and Implementation Solutions

Hadeeba Arfan<sup>1</sup>, Kashif Ayoub<sup>1</sup>, Azka Tariq Butt<sup>2</sup>, Fariha Munir<sup>3</sup>

<sup>1</sup> United Research Centre, Pakistan

<sup>2</sup> Rahbar Medical and Dental College, Lahore, Pakistan

<sup>3</sup> Senior Registrar, Akhtar Saeed Medical and Dental College, Lahore, Pakistan

## Abstract

**Background:** Metabolic dysfunction-associated steatotic liver disease (MASLD) affects approximately two-thirds of adults with type 2 diabetes (T2D), and about one in seven of those affected has advanced fibrosis. Effective fibrosis risk stratification is essential for identifying patients at risk of liver-related complications.

**Objective:** To critically appraise fibrosis risk-stratification tools in adults with T2D, identify gaps in routine care and propose practical implementation strategies.

**Methods:** A critical narrative review of evidence on non-invasive fibrosis tests, sequential diagnostic pathways and relevant therapeutic trials was undertaken. Direct T2D evidence was distinguished from mixed-cohort evidence and expert opinion. Literature selection was not systematic, and formal risk-of-bias assessment was not performed.

**Results:** FIB-4 remains an appropriate first-line triage test, but age-adjusted thresholds are needed in older adults, and poor rule-in sensitivity has been reported in a South Asian T2D cohort. Evidence that diabetes independently reduces test performance is inconsistent. Sequential testing with elastography or the Enhanced Liver Fibrosis test is guideline-supported, but prospective validation in T2D-only populations remains lacking. Semaglutide, resmetirom and dapagliflozin have shown histological benefit, while non-invasive monitoring of treatment-induced fibrosis regression remains unvalidated.

**Conclusion:** Fibrosis assessment should be integrated into routine diabetes care using existing tests and coordinated referral pathways. Prospective evaluation in T2D populations is needed to validate these pathways, rescreening intervals and treatment-monitoring strategies.

**Keywords:** MASLD; type 2 diabetes; liver fibrosis; FIB-4; non-invasive tests; transient elastography; Enhanced Liver Fibrosis test; resmetirom; semaglutide; SGLT2 inhibitors

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## 1. Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) is now the most common chronic liver disease worldwide. A systematic review of 92 population-based studies ( $n = 9,361,716$ ) estimated a pooled global prevalence of 30.05% across 1990–2019, rising from 25.26% in 1990–2006 to 38.00% in 2016–2019 [1]. The burden is concentrated in type 2 diabetes (T2D). An updated meta-analysis of 156 studies (1,832,125 patients) reported a pooled MASLD (then termed NAFLD) prevalence of 65.04% (95% CI 61.79–68.15%) in T2D, with clinically significant fibrosis (F2–F4) in 35.54% and advanced fibrosis (F3–F4) in 14.95% of those with steatotic liver disease [2]. An earlier meta-analysis restricted to 80 studies estimated a lower prevalence of 55.5% and, from only seven studies, an advanced-fibrosis prevalence of 17.0% (95% CI 7.2–34.8%) [3]. The divergence between these two estimates, and the extreme

heterogeneity reported in both ( $I^2 \approx 99$ –100%), should caution against quoting any single figure as a settled constant; the more defensible statement is that roughly half to two-thirds of adults with T2D have steatotic liver disease and that perhaps one in seven of them has advanced fibrosis.

In 2023, a multisociety Delphi process replaced “non-alcoholic fatty liver disease” with MASLD, defined by hepatic steatosis plus at least one cardiometabolic risk factor [4]. For people with T2D the practical consequence is simple: any person with T2D and steatosis meets the MASLD definition, and the new framework also recognises combined metabolic and alcohol-related disease (MetALD), which was previously excluded [5]. The renaming does not, however, change the biology or the diagnostic tools, and much of the evidence reviewed here was generated under NAFLD criteria. The authors use

MASLD throughout but retain original terminology where it defines a study population.

Fibrosis stage is the histological feature that carries prognostic weight. In a pooled analysis of five cohorts (1,495 patients, 17,452 patient-years), all-cause mortality rose stepwise with stage, and liver-related mortality rose steeply, with a rate ratio of 16.69 at F3 and 42.30 at F4 relative to F0 [6]. Single-cohort data are concordant: in an international cohort of 619 patients with long-term follow-up, fibrosis stage, but no other histological feature, was associated with overall mortality, transplantation and liver events [7], and in a Swedish cohort followed for up to 33 years fibrosis stage was the strongest predictor of disease-specific mortality [8]. A limitation often overlooked in reviews is that none of these cohorts was restricted to T2D, and the confidence intervals for stage-specific liver mortality are very wide; the prognostic primacy of fibrosis in T2D is therefore an extrapolation, albeit a reasonable one.

Detection is complicated by the poor sensitivity of routine liver enzymes. In 103 patients with T2D and normal aminotransferases, proton magnetic resonance spectroscopy identified steatotic liver disease in 50%, and 56% of those with steatotic liver disease had steatohepatitis [9]. Normal alanine aminotransferase (ALT) therefore cannot be used to exclude clinically important disease in T2D. Recognising this, the American Diabetes Association (ADA) 2025 consensus report now frames fibrosis screening in people with prediabetes or T2D, particularly with obesity, as a new standard of care and emphasises interprofessional management [10]. Care nevertheless remains divided between diabetology and hepatology, a structural problem that has been argued for some years to require a multidisciplinary model [11].

The therapeutic context has also shifted. Resmetirom improved fibrosis by at least one stage in patients with biopsy-confirmed steatohepatitis and F1B–F3 fibrosis in the phase 3 MAESTRO-NASH trial [12], and semaglutide 2.4 mg improved both steatohepatitis resolution and fibrosis in the phase 3 ESSENCE trial of F2–F3 disease [13]. Because glucagon-like peptide-1 receptor agonists (GLP-1RA) and sodium–glucose cotransporter-2 inhibitors (SGLT2i) are already widely prescribed in T2D, fibrosis assessment is no longer only prognostic; it now has direct treatment implications.

This narrative review critically appraises fibrosis risk-stratification tools from a T2D perspective, identifies where they fail in routine practice, and proposes implementation steps that can be delivered with existing tools. Scope is restricted to adults with T2D and to fibrosis rather than steatosis as the outcome of interest. As a narrative rather than systematic review, study selection was not exhaustive and was not formally risk-of-bias assessed; the strength of evidence for each claim is therefore stated explicitly in the text.

## 2. Pathophysiological Basis for Accelerated Fibrosis in T2D

### 2.1 Substrate Oversupply and Hepatic Lipotoxicity

In insulin-resistant states, adipose tissue fails to suppress lipolysis, so the flux of non-esterified fatty acids (NEFA) to the liver increases rather than decreases. Stable-isotope

tracing in patients with steatotic liver disease showed that 59.0% of hepatic triacylglycerol derived from circulating NEFA, 26.1% from de novo lipogenesis (DNL) and 14.9% from diet, and that DNL remained elevated in the fasting state [14]. Hyperinsulinaemia therefore drives hepatic DNL while adipose insulin resistance sustains NEFA delivery: two sources of lipid acting together. Within the hepatocyte, accumulation of diacylglycerol activates protein kinase C $\epsilon$ , which impairs insulin receptor signalling and perpetuates hepatic insulin resistance [15]. The critical caveat is that the tracer study enrolled only nine patients, not all with diabetes, and the diacylglycerol–PKC $\epsilon$  pathway explains insulin resistance better than it explains fibrosis. The link from lipotoxicity to fibrogenesis in humans with T2D remains largely inferential.

### 2.2 Inflammatory Amplification

Lipotoxic hepatocyte injury, together with adipose-derived cytokines, activates Kupffer cells and recruited macrophages, which release mediators that sustain steatohepatitis and signal to hepatic stellate cells [16]. Visceral adiposity and hypoadiponectinaemia, both common in T2D, favour this pro-inflammatory milieu [16]. The evidence here is largely associative in humans and mechanistic in rodents; no study has shown that the inflammatory profile of T2D independently predicts fibrosis progression after accounting for adiposity and steatohepatitis activity.

### 2.3 Stellate Cell Activation and the Role of Insulin Signalling

Activated hepatic stellate cells are the principal source of fibrillar collagen, and transforming growth factor- $\beta$  (TGF- $\beta$ ) is the dominant fibrogenic signal driving their transdifferentiation into myofibroblasts [17]. A recent study sought a direct link to insulin resistance: CRISPR knockout of the insulin-responsive portion of the insulin receptor in human LX-2 stellate cells increased cell growth and migration and altered transcriptional responses to TGF- $\beta$  [18]. In other words, reduced insulin receptor responsiveness enhanced stellate cell activation. This is a plausible mechanism by which insulin resistance may promote fibrosis, but it comes from a single immortalised cell line, and its relevance to human T2D has not yet been tested. It should be presented as hypothesis-generating rather than as proof that insulin resistance is itself fibrosis.

### 2.4 Gut–Liver Axis

In a prospective cohort of biopsy-characterised patients, a stool metagenomic signature distinguished advanced fibrosis from mild disease, with enrichment of Proteobacteria including *Escherichia coli* [19]. Translocated bacterial products are thought to act through Toll-like receptor 4 on Kupffer and stellate cells. However, the cohort was small and not restricted to T2D, and the signature is associative. Diabetes medications, notably metformin, also alter the microbiome, so disentangling disease from treatment effects in T2D is a major methodological obstacle that current studies have not overcome.

### 2.5 Genetic Modifiers

The PNPLA3 I148M and TM6SF2 E167K variants increase susceptibility to steatosis, steatohepatitis and fibrosis. In

large population cohorts their effects were amplified synergistically by adiposity [20], which is directly relevant to the obese T2D phenotype. Conversely, a protein-truncating HSD17B13 variant (rs72613567:TA) was associated with reduced risk of steatohepatitis and fibrosis [21]. Evidence that these gene effects are specifically magnified by diabetes, as opposed to adiposity, is limited, and genotyping has no current role in routine risk stratification.

## 2.6 Synthesis

Taken together, these pathways make it biologically plausible that fibrosis progresses faster in T2D than in metabolically healthier people with MASLD. The quality of this evidence is uneven: human data are mostly cross-sectional, mechanistic data are mostly preclinical, and few studies isolate diabetes from obesity. The main implication for this review is practical rather than mechanistic. If fibrosis biology differs in T2D, then tools derived in mixed MASLD cohorts may be systematically miscalibrated in T2D, which is the question Section II addresses.

## 3. Non-Invasive Fibrosis Stratification: The Evidence Through a T2D Lens

Non-invasive tests (NITs) are attractive because they avoid the morbidity, cost and sampling error of biopsy. Their performance, however, has been established mainly in hepatology cohorts in which T2D is a substantial minority rather than the defining characteristic. The largest individual patient data meta-analysis (37 studies,  $n = 5,735$ ) included 33% with T2D and a 30% prevalence of advanced fibrosis, a spectrum closer to secondary care than to a diabetes clinic [22]. This spectrum bias is the single most important lens through which the figures below should be read.

### 3.1 Serum-Based Tests

#### FIB-4 Index

FIB-4 is calculated as  $\text{age} \times \text{AST} / (\text{platelet count} \times \sqrt{\text{ALT}})$ . The widely used cut-offs of  $<1.30$  to exclude and  $>2.67$  to include advanced fibrosis were validated in a NAFLD cohort by Shah and colleagues [23], and FIB-4 is the recommended first step in all major guidelines. In the individual patient data meta-analysis, its area under the receiver operating characteristic curve (AUROC) for advanced fibrosis was 0.76, lower than that of transient elastography (0.85) [22].

Two T2D-relevant limitations are well documented. The first is age. In 634 biopsied patients, FIB-4 and NFS performed similarly across age bands above 35 years (AUROC 0.77–0.84), but specificity fell to 35% for FIB-4 in those aged 65 years or older; a revised lower cut-off of 2.0 in this group restored specificity to 70% with a sensitivity of 77% [24]. Because people with T2D are, on average, older, age-related false positives inflate referral burden. The second is diabetes itself, although the evidence is more nuanced than is often stated. In a pooled East Asian biopsy cohort of 1,906 patients, FIB-4 had a lower AUROC in T2D than without T2D (0.761 vs 0.821), but the difference disappeared after age-matching, and the authors concluded that FIB-4 retains screening value in people with T2D younger than 65 years [25]. In other

words, part of the apparent underperformance of FIB-4 in T2D is an age effect rather than a diabetes effect.

In India, a prospective study of 789 people with T2D and MASLD, using transient elastography rather than biopsy as the reference standard, found that the conventional rule-in cut-off of  $>2.67$  had a sensitivity of only 22.1% (specificity 92.2%); the optimal rule-in threshold was 1.68 (AUROC 0.69), and rule-out AUROCs were 0.586 for FIB-4 and 0.570 for NFS [26]. In a US cohort of 213 people with T2D who underwent magnetic resonance spectroscopy and biopsy, no clinical panel diagnosed advanced fibrosis significantly better than plasma AST alone [27]. Taken together, these studies support the conclusion that FIB-4 is a reasonable first-line triage tool in T2D but that its thresholds are population-specific and have not been validated across ethnic groups.

A mechanism frequently invoked in the literature, that metformin and statins suppress ALT and so falsely lower FIB-4, deserves correction. Because ALT sits in the denominator, a lower ALT would raise FIB-4, not lower it; any effect on AST would work in the opposite direction. We found no study quantifying the net effect of these drugs on FIB-4 classification in T2D, and this hypothesis should not be presented as established. What is established is that aminotransferases are an unreliable marker in T2D: in 561 outpatients with T2D screened by elastography, elevated ALT ( $\geq 40$  U/L) was present in only 28% of those with fibrosis [28].

#### NAFLD Fibrosis Score

The NFS was derived with impaired fasting glucose or diabetes as a component variable [29]. Consequently, every person with T2D begins with a higher score, which is expected to reduce specificity in diabetes populations. The individual patient data meta-analysis found NFS less accurate than FIB-4 overall (AUROC 0.73 vs 0.76) [22], and in the Indian T2D cohort its optimal rule-in AUROC was 0.619 [26]. There is little argument for using NFS in preference to FIB-4 in T2D.

#### Enhanced Liver Fibrosis Test

The Enhanced Liver Fibrosis (ELF) test combines hyaluronic acid, the amino-terminal propeptide of type III procollagen and tissue inhibitor of metalloproteinase-1, which reflect matrix turnover rather than hepatocellular injury, and it does not include age. A meta-analysis of 11 studies against biopsy found high sensitivity ( $>0.90$ ) for excluding advanced fibrosis at a threshold of 7.7, but limited specificity: a threshold of 10.18 was needed to reach 0.90 specificity, at which sensitivity fell to 0.57, and positive predictive value was poor in low-prevalence settings [30]. This is the key point for T2D screening, which is a lower-prevalence setting than hepatology clinics: ELF is best used as a rule-out test within a sequence, not as a stand-alone diagnostic. Its real-world value was shown in a UK primary care pathway of 3,012 patients using FIB-4 followed by ELF, which detected five times more advanced fibrosis and cirrhosis and reduced unnecessary referrals by 81% [31]. That study was not restricted to T2D, and no equivalent T2D-specific pathway evaluation was identified.

#### PRO-C3 and Other Direct Markers

PRO-C3, a marker of type III collagen formation, had the highest AUROC (0.90) for advanced fibrosis in the US T2D

biopsy cohort, although it did not significantly outperform AST [27]. It is not widely available and has no validated treatment-monitoring thresholds, so its role remains investigational.

### 3.2 Imaging-Based Tests

#### Vibration-Controlled Transient Elastography

Vibration-controlled transient elastography (VCTE) is the most widely validated imaging NIT. In a prospective UK multicentre study of 450 patients with suspected NAFLD, liver stiffness measurement (LSM) diagnosed  $F \geq F3$  with an AUROC of 0.80 (Youden cut-off 9.7 kPa) and cirrhosis with an AUROC of 0.89; in multivariable analysis, only fibrosis stage affected LSM, and neither steatosis nor probe type did [32]. This finding contradicts the commonly repeated claim that steatosis materially inflates LSM. The XL probe improves measurement success in obesity [33], which matters because many people with T2D are obese. Hepatic inflammation, recent food intake, congestion and cholestasis can raise LSM independently of fibrosis, and these are established sources of false positives [34].

In an unselected T2D outpatient population of 561 patients, VCTE identified steatosis in 70%, F2 in 6% and F3–F4 (LSM  $\geq 9.7$  kPa) in 9%, broadly concordant with FIB-4 and APRI estimates [28]. This is one of the few T2D-specific screening datasets and it supports systematic screening, but it comes from a single US region, and liver biopsy was performed only when results suggested fibrosis, which introduces verification bias.

#### Shear-Wave and Magnetic Resonance Elastography

Two-dimensional shear-wave elastography, available on conventional ultrasound platforms, has diagnostic performance broadly comparable to VCTE but is more operator-dependent and has less standardised cut-offs [34]. Magnetic resonance elastography (MRE) is the most accurate imaging method for staging fibrosis and is less affected by obesity, but cost and access restrict it to specialist centres [34]. MRI proton density fat fraction measures steatosis, not fibrosis, and should not be used as a fibrosis test.

### 3.3 Sequential Algorithms

Sequential testing, using a cheap first-line test to triage patients and a second test for those who remain indeterminate, is now the backbone of guidance from EASL (2021) [34], the joint EASL–EASD–EASO guideline (2024) [35], the AASLD practice guidance (2023) [36], the AGA clinical care pathway (2021) [37] and the ADA consensus (2025) [10]. In the individual patient data meta-analysis, FIB-4 ( $<1.3$ ;  $\geq 2.67$ ) followed by VCTE ( $<8.0$ ;  $\geq 10.0$  kPa) achieved a sensitivity of 66% and a specificity of 86%, with 33% of patients still requiring biopsy for a definitive diagnosis [22]. A one-third residual indeterminate rate in an unselected T2D population would generate substantial secondary-care demand, and none of these algorithms has been prospectively validated in a T2D-only population.

### 3.4 Liver Biopsy

Biopsy remains the reference standard but is itself an imperfect one. In 51 patients who had paired samples, fibrosis stage differed by one or more stages in 41%, and

35% of patients with bridging fibrosis on one core had mild or no fibrosis on the other [38]. This matters for NIT validation as well as clinical care: part of any NIT's apparent error is actually error in the reference standard. Clinically, biopsy should be reserved for persistently discordant or indeterminate NITs where management depends on the result, or for suspected alternative diagnoses. Nor is it a prerequisite for resmetirom: the US label specifies non-cirrhotic steatohepatitis with fibrosis “consistent with” stages F2–F3 and does not mandate histology [39].

## 4. Practical Gaps: Where Stratification Fails in Real-World T2D Care

### 4.1 Gap 1: Tools Not Calibrated for the T2D Population

The core problem is one of derivation. FIB-4 and NFS were derived and validated largely in hepatology cohorts, and the best meta-analytic data come from populations in which only a third had T2D and advanced fibrosis prevalence was 30% [22]. When the same thresholds are applied in older people with T2D, specificity collapses [24]; when they are applied in South Asian people with T2D, sensitivity at the rule-in cut-off collapses [26]. The East Asian biopsy data suggest that age rather than diabetes explains much of the performance gap [25], which is an important nuance: the solution may be age-adjusted rather than diabetes-specific thresholds. What is missing is a large, prospectively recruited, ethnically diverse T2D cohort with histology or a robust imaging reference standard. Until such data exist, T2D-specific cut-offs should be regarded as locally derived and provisional.

### 4.2 Gap 2: Screening Is Recommended but Not Operationalised

Guidance has converged. The ADA consensus report, the EASL–EASD–EASO guideline, the AASLD guidance and the AGA pathway all recommend fibrosis risk assessment in people with T2D, starting with FIB-4 [10,35–37]. The gap is therefore not an absence of recommendation, as is sometimes stated, but an absence of implementation infrastructure and of evidence on rescreening intervals. Recommended intervals for repeating FIB-4 in low-risk people rest on expert opinion rather than on prospective data on fibrosis progression in T2D. It is also unknown whether starting a GLP-1RA or SGLT2i should change the reassessment schedule.

### 4.3 Gap 3: Fragmented Specialty Care

Most people with T2D are managed in primary care or diabetology, where liver disease has not traditionally been tracked as a complication alongside retinopathy, nephropathy and neuropathy [10]. The multisystem nature of MASLD, which links liver, cardiovascular and renal outcomes, argues for integrated rather than sequential specialist care [11]. We did not identify controlled evaluations showing that joint diabetes–hepatology clinics improve hard outcomes; the case for them currently rests on process measures and face validity. This is a legitimate area for health-services research rather than a settled solution.

#### 4.4 Gap 4: Pharmacotherapy Creates a Moving Target

Several drugs now modify liver histology. In ESSENCE, semaglutide 2.4 mg achieved resolution of steatohepatitis without fibrosis worsening in 62.9% versus 34.3% with placebo, and fibrosis improvement without worsening of steatohepatitis in 36.8% versus 22.4%, at 72 weeks in patients with F2–F3 disease [13]. In MAESTRO-NASH, fibrosis improved by at least one stage in 24.2% (80 mg) and 25.9% (100 mg) of patients receiving resmetirom versus 14.2% with placebo at 52 weeks [12]. Among SGLT2 inhibitors, a Chinese multicentre trial of 154 adults with biopsy-proven steatohepatitis, with or without T2D, found fibrosis improvement without worsening of steatohepatitis in 45% of patients on dapagliflozin versus 20% on placebo at 48 weeks [40]. Evidence for empagliflozin in T2D is limited to reduced liver fat on MRI-PDFF over 20 weeks [41], and the liraglutide LEAN trial (n = 52) showed resolution of steatohepatitis and less fibrosis progression, but was a small phase 2 study not powered for fibrosis regression [42].

These data create a practical problem for monitoring. If FIB-4 or LSM improves after a year of treatment, the change may reflect genuine fibrosis regression, reduced inflammation or weight loss affecting the measurement, or regression to the mean. No NIT has been validated against paired biopsies as a measure of treatment response in T2D, and no guideline defines what constitutes a meaningful change. Reviews that recommend specific monitoring schedules should acknowledge that these are pragmatic proposals, not evidence-based standards.

#### 4.5 Gap 5: Equity of Access

FIB-4 costs almost nothing beyond routine blood tests, whereas VCTE requires dedicated equipment and trained operators and MRE is confined to specialist centres [34]. Access to second-line testing is therefore likely to be unequal between specialist and community settings and between high- and low-income health systems. Validation data are also unevenly distributed: the South Asian evidence shows how poorly imported thresholds can perform [26], and regional prevalence varies widely [1]. Quantitative data on screening rates by ethnicity, income or rurality in T2D are sparse, and this gap should be stated as a gap in evidence rather than filled with assumptions.

#### 4.6 Gap 6: Absence of an Integrated Care Pathway

Glycaemic control, cardiovascular risk, weight management and liver fibrosis are still managed as separate domains, even though GLP-1RA and SGLT2i act on all four. The ADA consensus explicitly calls for fibrosis screening to become a new standard of care in diabetes [10], but it does not yet specify how liver assessment should be embedded in drug initiation and follow-up. A person started on semaglutide for weight and glycaemia may therefore be receiving an effective liver treatment without any mechanism to document hepatic response.

### 5. Implementation Solutions: A Pragmatic Roadmap

The proposals below use tools that already exist. For each, we state whether it rests on direct evidence, indirect evidence from non-T2D populations, or expert judgement, because a common weakness of narrative reviews in this

field is to present pragmatic suggestions as if they were validated pathways.

#### 5.1 Solution 1: A Tiered Pathway Anchored in the Annual Diabetes Review

At the first tier, FIB-4 should be calculated at the annual diabetes review from blood tests that are already routinely taken. Low risk would be defined as FIB-4 <1.30 in people younger than 65 years and <2.0 in those aged 65 years or older, a threshold derived and validated in a European biopsy cohort [24] and consistent with current guidance [35]. At the second tier, people with indeterminate or high FIB-4 should undergo VCTE or ELF, as endorsed by the EASL–EASD–EASO guideline and the ADA consensus [10,35]. At the third tier, hepatology should assess people with high-risk LSM, discordant results or suspected cirrhosis, using MRE or biopsy where management depends on precise staging [34]. The structure is supported by direct evidence from a UK primary care pathway using FIB-4 followed by ELF, which increased detection of advanced fibrosis and cirrhosis fivefold and cut unnecessary referrals by 81% [31]. The evidence is indirect for T2D, since that pathway was not restricted to diabetes, and the age-adjusted threshold has not been validated in non-European T2D populations.

#### 5.2 Solution 2: Automated Scoring in the Electronic Health Record

Because age, AST, ALT and platelet count are already recorded, automatic FIB-4 calculation within diabetes review templates, with prompts for second-line testing when thresholds are exceeded, is technically simple. The UK pathway evaluation shows that structured decision support for NITs changes referral behaviour [31]. However, we did not identify a published evaluation of an automated FIB-4 alert specifically within diabetes care, and alert fatigue is a known risk of electronic prompts. This proposal is therefore supported by indirect evidence and should be introduced with an audit of uptake and downstream referral volumes. Claims in the literature about artificial-intelligence risk models outperforming FIB-4 in T2D should be treated with caution until externally validated.

#### 5.3 Solution 3: Shared Diabetes–Hepatology Care

The ADA consensus report explicitly advocates interprofessional management [10], and the multisystem burden of MASLD supports integrating diabetology, hepatology, cardiology and nutrition input [11]. In practice this could be a joint clinic, a virtual multidisciplinary meeting, or a hepatology advice-and-guidance service for primary care. Evidence for improved outcomes is currently limited to expert opinion and process data, so these models should be evaluated prospectively with outcomes such as time to diagnosis, appropriate referral rate and uptake of disease-modifying therapy.

#### 5.4 Solution 4: A Provisional Monitoring Framework During Pharmacotherapy

A reasonable interim approach is to record a baseline FIB-4, and LSM where available, before starting a GLP-1RA or SGLT2i in anyone with known or suspected MASLD, and to repeat the assessment after 12–18 months. For

resmetirom, the US label requires non-cirrhotic disease consistent with F2–F3, which can be established non-invasively [39]; the phase 3 efficacy data were generated with 52-week histological end points [12]. An apparent improvement in a single NIT should not by itself trigger de-escalation of monitoring, because no NIT has been validated as a measure of treatment-induced fibrosis regression in T2D. This framework is expert judgement and should be presented as such.

### 5.5 Solution 5: Equitable Access

FIB-4 is the most equitable first-line test because it requires no additional equipment or cost. Where VCTE is unavailable, FIB-4 followed by ELF is a validated alternative [31], and a decision-analytic model of UK community pathways estimated that FIB-4 followed by ELF reduced the cost per case of advanced fibrosis detected from £25,543 under standard care to £8,932 [43]. This analysis is model-based and depend on assumptions about treatment effect and adherence, and was not conducted in a low- or middle-income setting. Portable VCTE in community diabetes services is a plausible equity intervention, but its effect on detection in underserved groups has not been formally evaluated.

### 5.6 Solution 6: Harmonised Guidance

The major societies now agree on the principle of FIB-4-first sequential testing in T2D [10,34–37]. What remains unharmonised are age- and ethnicity-specific thresholds, rescreening intervals, and how liver assessment is built into the prescribing of GLP-1RA and SGLT2i. A joint diabetes–hepatology working group could address these points, and fibrosis assessment could be included as a quality indicator in diabetes care, in the same way as retinal and renal screening. These are policy recommendations and not evidence-derived conclusions.

## 6. Emerging Frontiers and Research Priorities

Several lines of development may change fibrosis stratification in T2D, but none is ready for routine use, and each should be judged by the same standard applied to established tests: external validation in T2D populations at realistic disease prevalence. Direct markers of collagen formation such as PRO-C3 performed well in one T2D biopsy cohort [27], but thresholds for diagnosis and for treatment response have not been defined. Proteomic, microRNA and metagenomic signatures have shown discrimination in discovery cohorts [19], yet most lack independent replication and none has been evaluated in a diabetes clinic. Deep-learning analysis of conventional ultrasound images is attractive because ultrasound is widely available, but published models require prospective validation against an accepted reference standard before any role in T2D screening can be claimed.

The most pressing clinical questions concern treatment. It is not known whether combining resmetirom with a GLP-1RA produces additive fibrosis regression, how NITs should be interpreted during weight-reducing therapy, or whether histological response in trials translates into fewer liver events in T2D. The phase 3 programmes of semaglutide and resmetirom include outcome phases that will partly address the last question [12,13]. We would prioritise three research needs: a prospective, multi-ethnic T2D cohort to derive and validate age- and

ethnicity-adjusted NIT thresholds; paired-biopsy studies defining what change in LSM or ELF reflects genuine fibrosis regression on treatment; and pragmatic trials of diabetes-embedded screening pathways with liver-related and cardiovascular outcomes.

## 7. Strengths and Limitations of This Review

This review focuses on a population in which the burden of advanced fibrosis is high and in which most of the practical decisions are made outside hepatology. It distinguishes, section by section, between direct T2D evidence, extrapolation from mixed MASLD cohorts, and expert opinion. Its limitations are those of the narrative format. Literature selection was not systematic and may be subject to selection bias. Study quality was not formally appraised with a tool such as QUADAS-2, so accuracy estimates are reported as published rather than bias-adjusted. Much of the underlying evidence was generated under NAFLD rather than MASLD definitions, and although the overlap is large, the populations are not identical. Finally, several important T2D-specific data sources come from single countries (the United States, India, and East Asia), which limits generalisability.

## 8. Conclusion

Steatotic liver disease is present in about two-thirds of adults with T2D, and roughly one in seven of those affected has advanced fibrosis. Fibrosis stage is the histological feature most strongly linked to liver-related mortality, although that link has been established in mixed MASLD cohorts rather than in cohorts of people with T2D alone. Normal aminotransferase levels do not exclude clinically significant disease in this population. The mechanisms thought to speed up fibrosis in T2D are biologically plausible but rest largely on cross-sectional human data and preclinical models. They do not yet explain why fibrosis progresses differently in T2D from how it progresses in obesity alone.

The evidence on non-invasive tests supports a narrower conclusion than is often drawn. FIB-4 remains a suitable first-line triage test in T2D, but its specificity falls in people aged 65 years or older unless an age-adjusted threshold is used. Part of its apparent underperformance in T2D is explained by age rather than by diabetes itself. Its conventional rule-in threshold showed poor sensitivity in a South Asian T2D cohort, and the NFS offers no advantage over FIB-4. ELF and transient elastography perform better as second-line tests. However, ELF has limited positive predictive value when prevalence is low, sequential algorithms still leave about one-third of patients unresolved, and none of these algorithms has been prospectively validated in a population made up only of people with T2D. Liver biopsy remains the reference standard, but it is imperfect because of sampling variability.

Semaglutide and resmetirom have shown histological benefit in phase 3 trials, and dapagliflozin has done so in a single randomised trial. However, no non-invasive test has been validated to measure fibrosis regression during treatment, so how to monitor these patients remains unresolved. Guidance from the major societies now agrees on FIB-4-first sequential testing in T2D. The remaining gaps are implementation, validated rescreening intervals,

thresholds for specific populations, and equitable access to second-line tests. Until prospective evidence from T2D populations addresses these gaps, the tiered pathway and monitoring approach proposed in this review should be treated as pragmatic interim measures rather than validated standards.

## Declarations

Ethics approval and consent to participate: Not applicable. This narrative review uses published literature and reports no newly recruited participants or individual-level patient data.

Consent for publication: Not applicable.

Data availability: This review uses data reported in the cited publications; no new primary dataset was generated.

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**Table 1. Reported performance of non-invasive tests for advanced fibrosis (F3–F4), mixed MASLD versus T2D cohorts. Values are as reported in the cited source; reference standards and populations differ, so values are not directly comparable across rows.**

| Test       | Components                                                | Mixed MASLD cohorts                                                          | T2D cohorts                                                                                                    | Main limitation in T2D                                               | Ref.          |
|------------|-----------------------------------------------------------|------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|---------------|
| FIB-4      | Age, AST, ALT, platelets                                  | AUROC 0.76 (IPD meta-analysis, n = 5,735; 33% T2D)                           | AUROC 0.761 (East Asian biopsy cohort); rule-in AUROC 0.69, sensitivity 22.1% at >2.67 (India, VCTE reference) | Specificity 35% at ≥65 years with standard cut-off; 2.0 restores 70% | [22,24–26]    |
| NFS        | Age, BMI, IFG/diabetes, AST/ALT ratio, platelets, albumin | AUROC 0.73                                                                   | Rule-in AUROC 0.619 (India, VCTE reference)                                                                    | Diabetes is a component variable                                     | [22,26,29]    |
| ELF        | Hyaluronic acid, PIIINP, TIMP-1                           | Sensitivity >0.90 at 7.7; specificity 0.90 requires 10.18 (sensitivity 0.57) | No T2D-specific accuracy study identified                                                                      | Low positive predictive value at low prevalence                      | [30]          |
| AST alone  | AST                                                       | —                                                                            | AUROC 0.85 (US biopsy cohort)                                                                                  | Not a stand-alone recommended test                                   | [27]          |
| PRO-C3     | Type III collagen formation                               | —                                                                            | AUROC 0.90 (US biopsy cohort)                                                                                  | Limited availability; no validated thresholds                        | [27]          |
| VCTE (LSM) | Liver stiffness, kPa                                      | AUROC 0.85 (IPD); 0.80 for F≥F3, Youden cut-off 9.7 kPa (UK)                 | Prevalence study only: F3–F4 in 9% of 561 outpatients                                                          | False elevation with inflammation, food, congestion, cholestasis     | [22,28,32,34] |
| MRE        | Liver stiffness, kPa                                      | Highest accuracy among imaging NITs                                          | No T2D-specific accuracy study identified                                                                      | Cost and access                                                      | [34]          |

AUROC, area under the receiver operating characteristic curve; ELF, Enhanced Liver Fibrosis; IFG, impaired fasting glucose; IPD, individual patient data; LSM, liver stiffness measurement; MRE, magnetic resonance elastography; NFS, NAFLD Fibrosis Score; PIIINP, amino-terminal propeptide of type III procollagen; TIMP-1, tissue inhibitor of metalloproteinase-1; VCTE, vibration-controlled transient elastography.

**Table 2. Randomised trials of drugs relevant to T2D with liver end points.**

| Drug (dose)                   | Trial and design                        | Population                                 | Duration | Key liver outcome, drug vs placebo/control                                                      | Ref. |
|-------------------------------|-----------------------------------------|--------------------------------------------|----------|-------------------------------------------------------------------------------------------------|------|
| Semaglutide 2.4 mg weekly     | ESSENCE, phase 3 RCT (interim, n = 800) | Biopsy-confirmed MASH, F2–F3               | 72 weeks | MASH resolution without fibrosis worsening 62.9% vs 34.3%; fibrosis improvement 36.8% vs 22.4%  | [13] |
| Resmetirom 80 or 100 mg daily | MAESTRO-NASH, phase 3 RCT (n = 966)     | Biopsy-confirmed NASH, F1B–F3              | 52 weeks | Fibrosis improvement ≥1 stage 24.2% and 25.9% vs 14.2%; NASH resolution 25.9% and 29.9% vs 9.7% | [12] |
| Dapagliflozin 10 mg daily     | Multicentre RCT, China (n = 154)        | Biopsy-confirmed MASH, with or without T2D | 48 weeks | Fibrosis improvement without MASH worsening 45% vs 20%; MASH resolution 23% vs 8%               | [40] |
| Empagliflozin 10 mg daily     | E-LIFT, RCT vs standard care (n = 50)   | T2D with NAFLD                             | 20 weeks | MRI-PDFF difference –4.0% vs standard care; no histology                                        | [41] |
| Liraglutide 1.8 mg daily      | LEAN, phase 2 RCT (n = 52)              | Biopsy-confirmed NASH                      | 48 weeks | NASH resolution 39% vs 9%; fibrosis progression 9% vs 36%                                       | [42] |

MASH, metabolic dysfunction-associated steatohepatitis; MRI-PDFF, magnetic resonance imaging proton density fat fraction; NASH, non-alcoholic steatohepatitis; RCT, randomised controlled trial.