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Review Article

Is FIB-4 Enough? A Critical Review of Non-Invasive Fibrosis Assessment in MASLD

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ABSTRACT

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a major cause of chronic liver disease, requiring reliable methods for early fibrosis detection. The Fibrosis-4 (FIB-4) index is widely used for initial risk stratification.

Objective: To critically review the diagnostic performance, strengths, limitations, and clinical applications of FIB-4 and other non-invasive fibrosis assessment methods in MASLD.

Review Methodology: FIB-4 offers an accessible, cost-effective first-line assessment but has limitations related to age, diabetes, disease prevalence, and clinical setting. Secondary tests, including vibration-controlled transient elastography, shear-wave elastography, the Enhanced Liver Fibrosis test, and magnetic resonance elastography, may improve diagnostic accuracy when used sequentially.

Conclusion: FIB-4 should guide risk stratification rather than serve as a standalone diagnostic tool. Integrated assessment pathways and appropriate follow-up are essential for identifying advanced fibrosis and improving clinical management.

Keywords: MASLD; FIB-4; hepatic fibrosis; non-invasive tests; VCTE; shear-wave elastography; magnetic resonance elastography; ELF; risk stratification; diagnostic accuracy.

INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD) is characterized by hepatic steatosis associated with at least one cardiometabolic risk factor. The terminology replaces the former designation of non-alcoholic fatty liver disease (NAFLD) within the updated nomenclature. The disease spectrum ranges from uncomplicated steatosis to metabolic dysfunction-associated steatohepatitis (MASH), progressive fibrosis, and cirrhosis. Among these manifestations, fibrosis stage is a major determinant of liver-related morbidity and mortality. Consequently, identifying patients with clinically significant or advanced fibrosis is an important objective in contemporary MASLD management [1,2].

Liver biopsy remains an important reference method when histological assessment is necessary. However, its invasive nature, sampling variability, cost, and potential complications limit its suitability for repeated assessment and large-scale screening. Non-invasive tests (NITs) have therefore become central to fibrosis risk stratification. They allow clinicians to identify patients who may require additional investigation while reducing unnecessary specialist referrals and invasive procedures [1–3]. The Fibrosis-4 (FIB-4) index is particularly attractive because it uses four routinely available parameters: age, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and platelet count.

Its simplicity makes it suitable for primary care, diabetes clinics, and other settings where dedicated imaging or specialist assessment may not be immediately accessible. Contemporary guidelines recommend FIB-4 as an initial assessment tool, followed by additional testing when the result or clinical context warrants further investigation [1,2]. Nevertheless, FIB-4 has important limitations. Its components are indirect markers rather than direct measurements of fibrosis, and its diagnostic performance varies with the selected threshold and the population being assessed. A low score may be reassuring in a low-prevalence population but less reliable in patients with type 2 diabetes mellitus (T2DM), multiple metabolic risk factors, or a high pre-test probability of advanced disease. The question, “Is FIB-4 enough?”, must therefore be considered in relation to its intended clinical purpose. A test that is useful for initial triage is not necessarily sufficient for definitive fibrosis staging. This review critically evaluates the diagnostic performance of FIB-4, examines factors that contribute to misclassification, and discusses the complementary roles of VCTE, SWE, MRE, and ELF in sequential fibrosis assessment.

REVIEW METHODOLOGY:

To This article is a structured narrative review and does not represent a systematic review with

de novo quantitative synthesis. Literature searches were updated through 8 September 2026. PubMed/MEDLINE was searched using combinations of the following terms: “MASLD,” “NAFLD,” “FIB-4,” “advanced fibrosis,” “diagnostic accuracy,” “VCTE,” “transient elastography,” “shear-wave elastography,” “MRE,” “magnetic resonance elastography,” “ELF,” and “type 2 diabetes.” The former term NAFLD was retained because many influential diagnostic studies were published before the introduction of MASLD nomenclature. Additional targeted searches were undertaken to identify relevant clinical practice guidelines, diagnostic meta-analyses, systematic reviews, prospective pathway studies, and large observational cohorts. Reference lists of major guidelines and relevant reviews were screened manually to identify additional publications. The evidence synthesis prioritized studies involving adults with MASLD or NAFLD that evaluated advanced fibrosis, generally defined as histological fibrosis stage F3 or higher. Studies reporting sensitivity, specificity, predictive values, area under the receiver operating characteristic curve (AUROC), or clinically relevant referral pathways were considered particularly informative. Quantitative estimates were extracted as reported in the cited publications. No new pooled estimates were calculated. Where predictive values are presented

as illustrative calculations, they are explicitly distinguished from observed study findings. As this is a narrative review, the search and selection process should not be interpreted as an exhaustive systematic review. Quantitative comparisons are presented cautiously because diagnostic performance depends on patient selection, disease prevalence, fibrosis reference standards, thresholds, and measurement quality.

Clinical Importance of Fibrosis Assessment in MASLD: MASLD encompasses a broad spectrum of liver disease, and hepatic steatosis alone does not establish the presence of advanced liver injury. The principal diagnostic target in this review is advanced fibrosis, generally corresponding to histological stage F3 or higher. Identifying this stage is important because advanced fibrosis is associated with an increased risk of liver-related complications and adverse clinical outcomes [1,2]. It is essential to distinguish steatosis, steatohepatitis, fibrosis probability, and liver stiffness. FIB-4 does not diagnose hepatic steatosis or MASH. Instead, it estimates the probability of advanced fibrosis from demographic and laboratory variables. Elastography methods estimate liver stiffness, which correlates with fibrosis but is not equivalent to histological collagen deposition. Liver stiffness can also be influenced by inflammation, cholestasis, hepatic congestion, and other physiological or pathological conditions.

Consequently, neither a serum score nor an isolated stiffness measurement should be interpreted without considering the patient's clinical context [1–3]. These distinctions support a sequential approach in which an accessible first-line test identifies patients requiring further assessment, while complementary tests refine the probability of clinically important fibrosis.

FIB-4: Calculation and Clinical Interpretation:

The FIB-4 index was originally developed to estimate liver fibrosis in patients with HIV and hepatitis C virus coinfection [8]. It was subsequently evaluated in other chronic liver disease populations, including patients with NAFLD. The formula is: $FIB-4 = (Age \times AST) / (Platelet\ count \times \sqrt{ALT})$, Where age is expressed in years, AST and ALT in U/L, and platelet count in $10^9/L$. FIB-4 combines variables associated with liver injury and disease severity but does not directly measure fibrosis. AST and ALT may remain within normal limits in patients with advanced disease. Platelet count may decrease with portal hypertension but can also be affected by unrelated haematological or systemic conditions. Age contributes directly to the score and can produce age-related misclassification [1–3]. Commonly used decision thresholds are: FIB-4 below 1.3: Lower probability of advanced fibrosis in most adults younger than 65 years.

FIB-4 from 1.3 to 2.67: Indeterminate probability requiring further interpretation. FIB-4 above 2.67: Higher probability of advanced fibrosis, generally warranting additional assessment. For adults older than 65 years, an age-adjusted low-risk threshold around 2.0 is commonly used. In adults younger than 35 years, diagnostic accuracy is reduced, and secondary assessment may be appropriate when metabolic risk factors or abnormal liver chemistries are present [1,2]. These thresholds are clinical decision points, not histological boundaries. A high score does not establish advanced fibrosis, and a low score does not completely exclude it. Interpretation should therefore emphasize probability and the appropriate next clinical action rather than treating the score as a definitive diagnosis.

Strengths of FIB-4: The principal strength of FIB-4 is its accessibility. It requires no specialized imaging equipment and can be calculated from routinely available blood test results. This makes it suitable for primary care, metabolic clinics, diabetes services, and large-scale case-finding programmes. FIB-4 can also be incorporated into electronic health records to support automated calculations, clinical alerts, and periodic reassessment. These features may improve the consistency of fibrosis-risk assessment, particularly when clinicians manage large populations with metabolic risk factors. FIB-4 is particularly useful as a first-stage test when the prevalence of

advanced fibrosis is relatively low. In this setting, its main purpose is to identify patients who may not require immediate specialist investigation, while directing patients with indeterminate or elevated scores towards additional testing. Prospective primary-care pathway research has demonstrated the value of combining FIB-4 with a secondary test such as ELF. Such pathways have improved the identification of advanced fibrosis and reduced unnecessary referrals compared with less structured approaches [5]. Economic modelling has also supported sequential NIT strategies. Crossan and colleagues reported that pathways using non-invasive fibrosis assessment could reduce specialist referrals and healthcare costs compared with referring all patients for specialist evaluation [6].

These findings do not establish FIB-4 as an accurate standalone staging method. Rather, they demonstrate the practical value of incorporating a simple first-stage test into a structured clinical pathway.

Limitations and Sources of Misclassification

1. Indirect assessment of fibrosis: FIB-4 does not directly measure liver stiffness or extracellular matrix deposition. Its components reflect biological processes associated with liver injury and disease severity but are not specific to fibrosis. Normal aminotransferase concentrations cannot exclude

advanced fibrosis, while reduced platelet counts may result from conditions unrelated to chronic liver disease. Consequently, false-negative and false-positive classifications remain possible.

2. The indeterminate range: The range of 1.3–2.67 is clinically important because FIB-4 alone cannot confidently classify patients within this interval. An indeterminate score should not be interpreted as evidence of mild fibrosis or absence of advanced disease. Secondary testing with VCTE, SWE, or ELF may help clarify risk. In selected patients, particularly those with lower overall clinical risk, a guideline-supported strategy involving intensified cardiometabolic management and subsequent reassessment may also be appropriate [1,2].

3. Age-related limitations

Because age is included in the FIB-4 formula, the score can increase with advancing age independently of changes in fibrosis. This can lead to false-positive classifications among older adults. An age-adjusted threshold around 2.0 is used in adults older than 65 years to improve interpretation. Conversely, FIB-4 performs less reliably in younger adults, particularly those below 35 years. Secondary assessment should therefore be considered when the clinical context indicates substantial risk despite a low numerical score [1,2].

4. False reassurance from a low FIB-4: A low FIB-4 reduces the probability of advanced fibrosis but does not eliminate it. This limitation is particularly important in patients with T2DM, multiple metabolic risk factors, persistent liver-test abnormalities, or a high pre-test probability of advanced disease. The 2026 bivariate meta-analysis by Ghosal and Ghosal included 14 studies involving 5,521 participants. At the FIB-4 threshold of 1.3, pooled sensitivity was 73% and specificity was 69% [7]. These findings indicate that the threshold cannot be interpreted as an absolute exclusion test. Predictive values also depend on disease prevalence. Using sensitivity of 73% and specificity of 69% as an illustrative model, the estimated negative predictive value is approximately 98% at a 5% prevalence of advanced fibrosis, 96% at 10%, 91% at 20%, and 86% at 30%.

These figures are mathematical illustrations based on the stated sensitivity, specificity, and assumed prevalence. They are not observed predictive values from the meta-analysis. They demonstrate why a low score can be more reassuring in a low-prevalence population than in a high-risk specialist setting. Accordingly, a low FIB-4 should not automatically end the assessment when clinical suspicion remains high. In selected high-risk patients, secondary testing may be justified despite a score below 1.3.

5. False-positive classification: An elevated FIB-4 does not confirm advanced fibrosis. Older age, transient aminotransferase elevations, and thrombocytopenia unrelated to liver disease can increase the score. Patients with elevated values should undergo appropriate secondary assessment, with consideration of alternative explanations for the laboratory abnormalities. This reduces the risk of unnecessary referral or incorrect disease classification.

6. Acute illness and laboratory confounding: FIB-4 should not be relied upon during acute illness because AST, ALT, and platelet concentrations may change independently of chronic fibrosis. AASLD guidance advises against using the score in acutely ill patients [2]. Where clinically appropriate, reassessment after recovery may provide a more representative estimate of chronic fibrosis risk.

7. Diagnostic Performance: Rule-Out Versus Rule-In: The diagnostic value of FIB-4 depends on the intended purpose of the threshold. Lower thresholds generally prioritize sensitivity, whereas higher thresholds prioritize specificity. A threshold should therefore be interpreted in relation to the target condition and the consequences of false-negative and false-positive results. Wilson and colleagues conducted a systematic review and meta-analysis involving 207 studies and more than 80,000 patient investigations [12]. For advanced fibrosis, a FIB-4

threshold of 1.3 had a reported sensitivity of approximately 71%. A threshold of 2.67 had specificity of approximately 96%, but sensitivity was substantially lower, at approximately 32%.

These results illustrate the trade-off between the thresholds. The lower threshold is more appropriate for initial risk stratification, while the higher threshold identifies a smaller group with an increased probability of advanced fibrosis. Neither threshold provides definitive histological classification. The same meta-analysis reported that a lower threshold of 0.75 increased sensitivity to approximately 88%, although lower thresholds generally classify more patients as requiring additional assessment [12]. This illustrates the need to balance missed disease against the additional investigations generated by a more sensitive strategy. The 2026 meta-analysis by Ghosal and Ghosal reported pooled sensitivity of 73% and specificity of 69% at the 1.3 threshold [7]. The authors also identified regional variation in specificity, although the number of Indian cohorts was limited. These findings support further validation of thresholds across different populations rather than assuming uniform performance. Evidence from patients with T2DM further highlights the limitations of FIB-4. A 2024 systematic review and meta-analysis of 12 studies involving 5,624 patients with NAFLD and T2DM reported sensitivity of 0.74 and specificity of 0.62

for lower FIB-4 thresholds. At higher thresholds, sensitivity decreased to 0.33 while specificity increased to 0.92. The reported predictive values also varied substantially according to threshold and disease prevalence [11]. AUROC provides an additional measure of diagnostic discrimination. A 2024 meta-analysis of 86 studies involving 46,514 participants reported a summary AUROC of 0.81 for FIB-4 and 0.87 for ELF in assessing advanced fibrosis [10]. However, AUROC summarizes performance across thresholds and does not establish that a particular decision threshold is clinically safe in every population. Overall, FIB-4 provides useful initial risk stratification but should not be treated as a universal standalone fibrosis-staging test. Its interpretation should incorporate the clinical setting, disease prevalence, threshold-specific performance, and need for additional assessment.

8. Vibration-Controlled Transient Elastography:

Vibration-controlled transient elastography (VCTE) is a commonly used second-line method that estimates liver stiffness without requiring MRI infrastructure. In a 2024 systematic review and meta-analysis, Chon and colleagues reported an AUROC of approximately 0.87 for VCTE in detecting advanced fibrosis ($\geq F3$), with pooled sensitivity of 0.81 and specificity of 0.79 [13]. These findings support its use as a complementary test when FIB-4 is indeterminate or elevated. VCTE has practical advantages, including relatively rapid acquisition and suitability for outpatient assessment.

Nevertheless, liver stiffness is influenced by factors other than fibrosis. Inflammation, cholestasis, hepatic congestion, and recent food intake can affect measurements. Obesity, probe selection, acquisition technique, and operator experience may also influence reliability [3,13]. Measurement quality should be assessed before interpreting a VCTE result. Technically unreliable or clinically discordant measurements may require repeat acquisition, an alternative modality, or specialist evaluation. VCTE therefore complements rather than replaces FIB-4. A high stiffness value should be interpreted in the context of possible confounders, while a technically unreliable or unexpectedly low measurement should not override substantial clinical suspicion.

9. Shear-Wave Elastography: Shear-wave elastography includes point shear-wave elastography (pSWE) and two-dimensional shear-wave elastography (2D-SWE). These techniques estimate tissue stiffness using ultrasound-based methods and can be incorporated into appropriate ultrasound examinations. A 2025 meta-analysis included 13 pSWE studies involving 1,527 patients and nine 2D-SWE studies involving 1,088 patients. For advanced fibrosis, the summary receiver operating characteristic area was approximately 0.91 for pSWE and 0.85 for 2D-SWE [14]. These results suggest that SWE can contribute useful

information to fibrosis assessment. However, the estimates should not be interpreted as evidence that all SWE methods are interchangeable or universally superior to other tests. Thresholds depend on the device, acquisition method, study population, and reference standard. Operator training and measurement quality remain important, and interpretation should follow validated, modality-specific protocols. SWE may be particularly useful where ultrasound expertise is available but VCTE is not.

Threshold or context	Interpretation	Recommended action
FIB-4 <1.3 in adults younger than 65 years	Lower probability of advanced fibrosis; disease is not completely excluded	Continue metabolic risk management and reassess according to clinical risk [1,2].
FIB-4 1.3–2.67	Indeterminate probability	Consider VCTE, SWE, or ELF; selected patients may undergo risk-factor management and repeat assessment according to the applicable pathway [1,2].
FIB-4 >2.67	Higher probability of advanced fibrosis	Arrange secondary assessment and consider specialist referral [2].
Age >65 years	Age can increase the score independently of fibrosis	Apply age-adjusted interpretation; a low-risk threshold around 2.0 is used in guidance [1,2].
Age <35 years	Reduced diagnostic accuracy	Consider secondary testing when metabolic risk or abnormal liver chemistries are present [1,2].
Acute illness	Laboratory changes may distort the score	Do not rely on FIB-4 during acute illness; reassess when clinically appropriate [2].

Table 1. FIB-4 thresholds, interpretation, and recommended clinical action

Test	Representative evidence	Major advantage	Important limitation
FIB-4	Sensitivity approximately 71% at 1.3 and specificity approximately 96% at 2.67 in a 2025 meta-analysis [12]	Inexpensive and widely available	Indirect assessment; false negatives and false positives
VCTE	AUROC approximately 0.87 for $\geq F3$ fibrosis [13]	Rapid, non-invasive assessment	Technical limitations and non-fibrotic influences on stiffness
pSWE/2D-SWE	SROC AUC approximately 0.91 for pSWE and 0.85 for 2D-SWE for advanced fibrosis [14]	Can be incorporated into ultrasound examinations	Device-specific thresholds and operator dependence
MRE	AUROC approximately 0.89 for $\geq F3$ fibrosis in a 2024 meta-analysis [13]	High diagnostic discrimination	Cost and limited availability
ELF	Summary AUROC approximately 0.87 for advanced fibrosis [10]	Blood-based assessment with a different biological signal	Cost, availability, and pathway-specific interpretation

Table 2. Comparative characteristics of non-invasive fibrosis tests

10. Magnetic Resonance Elastography:

Magnetic resonance elastography (MRE) is an imaging-based method that estimates liver stiffness using MRI technology. It offers high diagnostic accuracy but is generally more expensive and less accessible than FIB-4 or ultrasound-based elastography. Chon and colleagues reported an AUROC of approximately 0.89 for MRE in detecting advanced fibrosis in their 2024 meta-analysis [13]. Other pooled analyses have also demonstrated good diagnostic

performance, supporting its role in selected patients requiring further clarification [15,16]. MRE is particularly useful when initial tests produce discordant results, when ultrasound-based elastography is technically unreliable, or when clinical suspicion remains high despite apparently reassuring first-line results. Its cost and infrastructure requirements limit its suitability for universal first-line assessment. MRE should therefore be viewed as a problem-solving modality rather than a replacement for accessible first-stage tests.

11. Enhanced Liver Fibrosis Test and Other Serum Biomarkers:

The Enhanced Liver Fibrosis (ELF) test combines serum biomarkers associated with extracellular matrix turnover. Unlike FIB-4, which relies on age and routine laboratory parameters, ELF provides information from fibrosis-related biological processes. This difference makes ELF a useful complementary test when elastography is unavailable, impractical, or inconclusive [1,2,4]. A 2024 meta-analysis involving 86 studies and 46,514 participants reported a summary AUROC of approximately 0.87 for ELF in assessing advanced fibrosis, compared with 0.81 for FIB-4 [10]. These estimates support the use of ELF as a secondary risk-stratification tool but do not establish it as a universal replacement for imaging-based assessment. ELF thresholds must be interpreted according to the assay, validated pathway, and intended clinical endpoint. AASLD guidance notes that an ELF value above 11.3 is

associated with increased risk of hepatic decompensation in patients with advanced fibrosis or cirrhosis [2]. This prognostic association should not be interpreted as a universal diagnostic threshold for all fibrosis stages.

12. Comparative Evaluation of Non-Invasive Tests:

The different NITs address related but distinct aspects of fibrosis assessment. FIB-4 estimates probability using demographic and laboratory variables. VCTE and SWE estimate liver stiffness using ultrasound-based methods. MRE assesses stiffness through MRI, while ELF measures serum markers associated with extracellular matrix turnover. The main advantage of FIB-4 is accessibility. Its limitations include indirect measurement, age-related effects, an indeterminate range, and imperfect sensitivity. VCTE offers practical second-line assessment but can be affected by technical limitations and non-fibrotic causes of increased stiffness. SWE provides an alternative ultrasound-based method, although its thresholds are device-specific. MRE offers high diagnostic accuracy but requires greater resources. ELF provides a complementary blood-based assessment but may have availability and cost limitations. The comparative meta-analysis by Wilson and colleagues also identified important methodological limitations, including concerns about the risk of bias in many imaging-

Assumed prevalence of advanced fibrosis	Estimated PPV	Estimated NPV	Clinical implication
5%	11%	98%	A negative result is highly reassuring, but most positive results may require confirmation.
10%	21%	96%	A negative result remains reassuring in this illustrative setting.
20%	37%	91%	Residual risk after a negative result becomes more important.
30%	50%	86%	A negative result provides less reassurance in a high-prevalence population.

Table 3. Illustrative effect of disease prevalence on predictive values

based studies [12]. Consequently, differences in reported diagnostic accuracy should not be interpreted without considering study design, patient selection, reference standards, and threshold selection. The strongest justification for sequential testing is that the methods provide complementary information. FIB-4 is suitable for initial triage, secondary testing refines risk, and MRE can help resolve selected difficult cases. This strategy balances accessibility, diagnostic uncertainty, and resource use.

13. Sequential Testing Algorithm: A sequential testing pathway is recommended for identifying patients with metabolic dysfunction-associated steatotic liver disease (MASLD) who may have advanced fibrosis. The European Association for the Study of the Liver, European Association for the Study of Diabetes, and European Association for the

Study of Obesity (EASL-EASD-EASO) recommend targeted fibrosis assessment, particularly in individuals with type 2 diabetes mellitus (T2DM), abdominal obesity accompanied by additional cardiometabolic risk factors, or persistently elevated liver enzymes [1]. The American Association for the Study of Liver Diseases (AASLD) similarly emphasizes fibrosis risk assessment in patients with metabolic risk factors and persistent liver-test abnormalities [2]. The FIB-4 index can be used as the initial assessment because it is inexpensive and calculated from routinely available laboratory parameters. Patients with FIB-4 below 1.3 generally have a lower probability of advanced fibrosis and may continue primary-level management with periodic reassessment according to their individual risk profile. More frequent reassessment may be appropriate for patients with T2DM, prediabetes, or multiple metabolic risk factors [2]. Patients with FIB-4 ≥ 1.3 generally require consideration of a second-line non-invasive test, such as vibration-controlled transient elastography (VCTE) or the Enhanced Liver Fibrosis (ELF) test [2]. Shear-wave elastography (SWE) may be considered where appropriate expertise and validated protocols are available. For selected patients in the indeterminate range, EASL-EASD-EASO guidance also supports intensified cardiometabolic risk management

followed by repeat assessment, depending on clinical risk and available resources [1]. Patients with FIB-4 > 2.67 have a higher probability of advanced fibrosis and should undergo further assessment and consideration of specialist referral. When results from FIB-4 and secondary testing are discordant, clinicians should reassess the patient's clinical risk, laboratory validity, measurement quality, and potential confounding factors. Magnetic resonance elastography (MRE) may be useful when uncertainty persists and more accurate fibrosis assessment is likely to influence clinical management [2]. The sequential approach combines the accessibility of FIB-4 with the additional diagnostic information provided by elastography or serum biomarkers. This strategy can improve risk stratification, support appropriate referral decisions, and reduce unnecessary specialist investigations. However, the final interpretation should always incorporate the patient's clinical presentation and the limitations of the individual tests.

14. Special Populations and Clinical Settings

14.1 Type 2 Diabetes Mellitus: Patients with T2DM represent an important group for fibrosis assessment because they have an increased prevalence of advanced fibrosis and may be at greater risk of disease progression. Current guidelines emphasize the importance of identifying fibrosis in this population and recommend appropriate follow-up based on individual metabolic risk [1,2].

A 2024 systematic review and meta-analysis involving 12 studies and 5,624 patients with NAFLD and T2DM reported pooled sensitivity of 0.74 and specificity of 0.62 for lower FIB-4 thresholds. At higher thresholds, sensitivity decreased to 0.33, while specificity increased to 0.92 [11]. These findings demonstrate that the diagnostic performance of FIB-4 remains imperfect in patients with diabetes and that a low score may not exclude advanced fibrosis in every individual. Consequently, FIB-4 should be used as an initial risk-stratification tool rather than an absolute exclusion test in patients with T2DM. Secondary assessment using VCTE, SWE, or ELF may be appropriate when additional risk factors are present, including persistent liver-test abnormalities, multiple cardiometabolic risk factors, or substantial clinical suspicion of advanced liver disease. Periodic reassessment is also important because metabolic risk and fibrosis probability may change over time.

14.2 Older Adults: Age is an important determinant of FIB-4 because it forms part of the calculation. Consequently, older adults may have elevated scores even when other laboratory parameters remain relatively stable, increasing the possibility of false-positive classification. To improve interpretation, an age-adjusted low-risk threshold around 2.0 is commonly used in adults

older than 65 years [1,2]. This adjustment should be applied according to the relevant guideline and clinical pathway. Elevated scores should not automatically be interpreted as evidence of advanced fibrosis; secondary testing may be necessary to clarify the underlying risk.

14.3 Younger Adults: FIB-4 has reduced diagnostic accuracy in adults younger than 35 years, partly because age contributes directly to the score and may result in relatively low values despite the presence of metabolic risk factors. Therefore, a low FIB-4 result should be interpreted cautiously when clinical suspicion remains high. In younger adults with significant metabolic risk, persistent abnormalities in liver enzymes, or other clinical features suggesting chronic liver disease, secondary assessment using elastography or an appropriate serum biomarker may be warranted [1,2]. Clinical judgement is particularly important in this population because conventional FIB-4 thresholds may not reliably identify all individuals requiring further evaluation.

14.4 Persistent Abnormal Liver Tests: Persistent elevation of aminotransferases warrants further evaluation, regardless of the FIB-4 result. Although AST and ALT contribute to the calculation, their concentrations do not directly measure fibrosis severity. Normal aminotransferase levels do not exclude advanced fibrosis, while elevated values may

occur because of acute inflammation, medication effects, or other hepatic and extrahepatic conditions. AASLD guidance recommends further evaluation when aminotransferase elevations persist for more than six months, including assessment for alternative causes of liver disease where appropriate [2]. FIB-4 should therefore be interpreted alongside the duration and pattern of liver-test abnormalities, clinical history, and other relevant investigations rather than used as the sole basis for clinical decisions.

14.5 Primary Care Versus Hepatology Settings:

The clinical interpretation of FIB-4 depends substantially on the population being assessed. In primary care, where the prevalence of advanced fibrosis may be relatively low, FIB-4 can be useful for identifying patients who are unlikely to have advanced disease and prioritizing those who need further testing. In hepatology settings, the prevalence of advanced fibrosis is generally higher, and a low FIB-4 may provide less reassurance. Sequential testing is therefore particularly valuable when patients are assessed in different healthcare settings. Primary care pathways can use FIB-4 to support initial triage, while VCTE, SWE, or ELF can refine the assessment of patients with indeterminate or elevated results. MRE may be considered in selected specialist cases when the results of initial tests remain inconclusive or

clinical suspicion is high [2]. Prospective pathway studies and economic evaluations support the potential value of structured fibrosis assessment in primary care by improving case identification and reducing unnecessary specialist referrals [5,6]. Nevertheless, pathway selection should account for local resources, disease prevalence, and the clinical consequences of missed advanced fibrosis.

15. Multidisciplinary and Allied Health Implications:

The assessment of fibrosis in MASLD requires coordination among clinicians, laboratory professionals, imaging specialists, dietitians, and other allied-health professionals. A structured multidisciplinary pathway can improve the quality of risk assessment by ensuring that laboratory measurements, test interpretation, secondary investigations, and referral decisions are appropriately coordinated. Laboratory professionals contribute by ensuring the analytical quality of AST, ALT, and platelet measurements, which are essential for accurate FIB-4 calculation. Imaging professionals contribute to the acquisition and quality assessment of VCTE and SWE measurements, while clinicians integrate the findings with the patient's medical history, metabolic risk factors, and clinical presentation. Dietitians and exercise professionals also have important roles in supporting lifestyle modification and cardiometabolic risk management. Appropriate nutrition, physical activity, weight management, and control of diabetes

and other metabolic abnormalities form essential components of comprehensive MASLD care, irrespective of the fibrosis-risk category. Electronic health records may further support implementation by automating FIB-4 calculation, generating reminders for periodic reassessment, and identifying patients who meet criteria for secondary testing. Standardized referral criteria can help ensure that patients with elevated risk, technically unreliable measurements, or discordant test results receive appropriate evaluation. For allied-health settings, the principal objective is to translate non-invasive test results into a reproducible clinical pathway. FIB-4 should be regarded as a risk-stratification instrument rather than a definitive diagnosis, and decisions regarding further investigation should be based on validated protocols and appropriate clinical oversight.

16. Research Gaps and Future Directions:

Further research is required to improve the accuracy and clinical utility of non-invasive fibrosis assessment in MASLD. First, FIB-4 thresholds require additional validation across different age groups, diabetes status, geographical regions, and healthcare settings. Differences in disease prevalence and population characteristics may influence sensitivity, specificity, and predictive values. Although recent meta-analytic

evidence suggests regional variation in diagnostic performance, further studies involving South Asian populations are needed before population-specific thresholds can be recommended [7]. Second, the indeterminate FIB-4 range remains a major challenge in clinical practice. A substantial proportion of patients may require secondary testing, creating additional costs and demands on imaging and specialist services. Future studies should evaluate strategies that combine FIB-4 with clinical risk factors, additional serum biomarkers, longitudinal laboratory changes, and electronic health record data to improve patient selection for secondary assessment. Third, future investigations should evaluate clinical outcomes rather than diagnostic accuracy alone. Although AUROC, sensitivity, and specificity are important, the most useful pathway is one that identifies patients who benefit from further evaluation and management while minimizing missed advanced fibrosis, unnecessary investigations, and avoidable referrals. Studies should therefore assess referral burden, time to diagnosis, cost-effectiveness, patient outcomes, and the consequences of false-negative classifications. Fourth, implementation studies should compare sequential testing pathways across primary care, diabetes clinics, and hepatology services. Such studies should use clearly defined fibrosis endpoints, appropriate reference standards, and transparent reporting of thresholds and measurement quality. Particular attention should be given to the feasibility of

implementing sequential pathways in settings where access to VCTE, SWE, ELF, or MRE is limited. Finally, further evidence is required to clarify how different NITs should be combined and interpreted. VCTE, pSWE, 2D-SWE, MRE, and ELF differ in their measurement principles, availability, and technical limitations. Their thresholds should not be considered interchangeable without appropriate validation. Future research should establish which combinations provide the greatest clinical benefit for different patient populations and healthcare systems. Overall, progress in MASLD fibrosis assessment will depend not only on improving individual tests but also on developing accessible, validated, and clinically effective pathways that integrate non-invasive testing with appropriate follow-up and metabolic risk management.

CONCLUSION: FIB-4 is a practical, accessible, and cost-effective first-line tool for stratifying the risk of advanced liver fibrosis in patients with metabolic dysfunction-associated steatotic liver disease (MASLD). However, its diagnostic performance varies according to age, diabetes status, disease prevalence, and clinical setting. Therefore, a low FIB-4 score should not be interpreted as an absolute exclusion of advanced fibrosis, particularly in high-risk patients. A sequential approach combining FIB-4 with

secondary non-invasive tests, such as vibration-controlled transient elastography (VCTE), shear-wave elastography (SWE), or the Enhanced Liver Fibrosis (ELF) test, can improve risk assessment and guide appropriate referral. Magnetic resonance elastography (MRE) may be considered when initial results are indeterminate or discordant. Ultimately, FIB-4 should be used as part of an integrated clinical pathway rather than as a standalone diagnostic test. Effective implementation requires appropriate follow-up, periodic reassessment, multidisciplinary collaboration, and further validation across diverse populations to improve the early identification and management of advanced fibrosis in MASLD.

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