



Metabolic Dysfunction-Associated Steatotic Liver Disease in Type 2 Diabetes: A Narrative Review of Who Needs Fibrosis Staging and When

Davide Carrara^{1*}, Nadine Zumbrunn² and Gergely Torok³

¹Department of Hepatology, Apulian University Hospital, Lecce, Italy

²Department of Radiology, Lemanic Institute of Diabetes Research, Lausanne, Switzerland

³Department of Endocrinology, Balaton Institute of Diabetes Care, Veszprem, Hungary

*Correspondence to: Davide Carrara, Department of Hepatology, Apulian University Hospital, Lecce, Italy

Received: 17 January 2023; Accepted: 14 May 2023; Published: 22 September 2023

Copyright: © 2023 Carrara D. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Steatotic liver disease is present in a majority of people with type 2 diabetes, and guidance now recommends that they be screened for the fibrosis that determines whether it matters. The recommended first step is FIB-4, a score calculated from age, transaminases and platelet count, with a value below 1.30 taken to exclude advanced fibrosis and anything above it triggering elastography or a serum marker. The difficulty is that FIB-4 performs modestly in this population. In 149 patients with type 2 diabetes and steatotic liver disease, elastography identified advanced fibrosis in 7.4 per cent and some degree of fibrosis in 75.8 per cent, while four non-invasive scores applied to the same people flagged 14.1, 8.7, 5.4 and 3.4 per cent as high risk. Reported areas under the curve for FIB-4 in diabetes cohorts are 0.711 and 0.735, against 0.936 for an elastography-based index. In primary care, screening 308 patients found 59 per cent with steatotic liver disease, 7 per cent with suspected advanced fibrosis and 1.9 per cent with cirrhosis. This review sets out what the pathway detects and where it is weakest.

Keywords: Steatotic liver disease; Type 2 diabetes; Liver fibrosis; FIB-4; Transient elastography

Introduction

Metabolic dysfunction-associated steatotic liver disease is the term adopted in 2023 for hepatic steatosis occurring alongside cardiometabolic risk factors, replacing the earlier nomenclature built on the exclusion of alcohol [1,2]. Type 2 diabetes is itself one of the qualifying criteria, so essentially every person with fatty liver and diabetes meets the definition [1,3].

Prevalence is high. Steatotic liver disease affects up to 30 per cent of the general adult population and up to 70 per cent of people with type 2 diabetes, and exceeds half in those with additional metabolic comorbidity [3,4,5]. The clinically important variable is not steatosis but fibrosis, which is what predicts cirrhosis, hepatocellular carcinoma and liver-related mortality [6,7,27,28]. Systematic screening in diabetes outpatient settings has been argued for on exactly that basis [29,30,31].

Guidance from the hepatology, diabetes and endocrine societies now recommends that people with type 2 diabetes be

assessed for advanced fibrosis using a stepwise non-invasive pathway [8,9,10]. This review examines what that pathway finds, how well its first step performs in this particular population, and where the recommendations disagree.

Material and Methods

Search strategy: PubMed and the archives of the major hepatology, diabetes and endocrinology journals were searched for studies of fibrosis assessment in type 2 diabetes. Search terms combined steatotic liver disease, NAFLD and MASLD with type 2 diabetes, FIB-4, NAFLD fibrosis score, transient elastography, liver stiffness and screening. Reference lists of the principal guidelines [8,9,10] were screened by hand for primary sources.

Eligibility: Studies were included if they reported the prevalence of steatotic liver disease or fibrosis in populations with type 2 diabetes, evaluated a non-invasive test against a reference standard, or set out a screening pathway. Studies in

mixed populations are cited where diabetes-specific data are reported and are identified as such.

Data extraction and handling: Design, setting, sample size, the reference standard used and the reported estimate were extracted as published. The reference standard is stated alongside every accuracy figure, because biopsy-based and elastography-based estimates are not interchangeable, and the method used to define fibrosis determines the prevalence reported. No pooling or re-analysis was performed. Figures 1 to 6 and Tables 1 to 3 reproduce published values only. This is a narrative synthesis and was not registered as a systematic review.

Results

What screening finds in primary care: A prospective study offered assessment to 308 people with type 2 diabetes in primary care. Steatotic liver disease was present in 59 per cent, suspected advanced fibrosis, defined as a liver stiffness measurement of 10 kPa or above, in 7 per cent, and findings consistent with cirrhosis in 1.9 per cent (Figures 2 and 5) [11]. Those proportions define the clinical problem: the majority have the disease, a small minority have the stage of it that changes management.

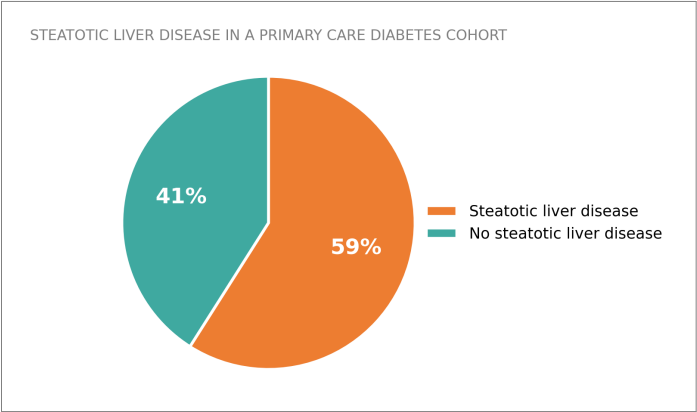


Figure 2: Steatotic liver disease in a primary care diabetes cohort [11]

The recommended pathway: The stepwise approach begins with FIB-4, calculated from age, aspartate and alanine transaminase and platelet count. A value below 1.30 is taken to make advanced fibrosis unlikely and no further testing is advised. A value of 1.30 or above triggers a second-line assessment, either vibration-controlled transient elastography or the enhanced liver fibrosis serum test, whose accuracy has been assessed in meta-analysis [22], with liver stiffness thresholds around 8, 10 and 15 kPa marking increasing probability of advanced disease and referral to hepatology (Figure 3, Table 1) [8,9,12].

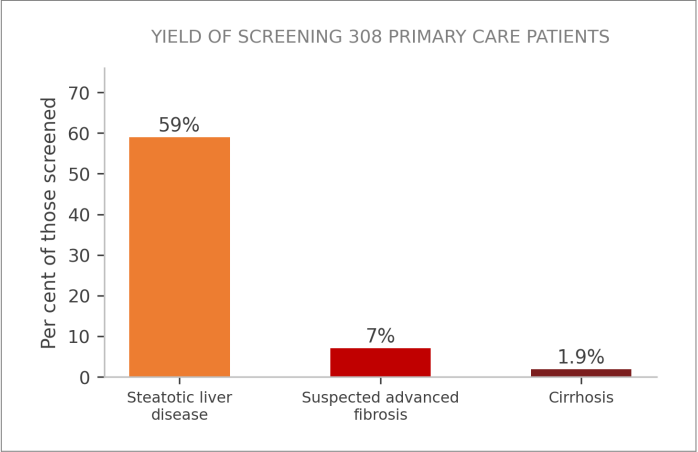


Figure 5: Yield of screening 308 primary care patients with type 2 diabetes [11]

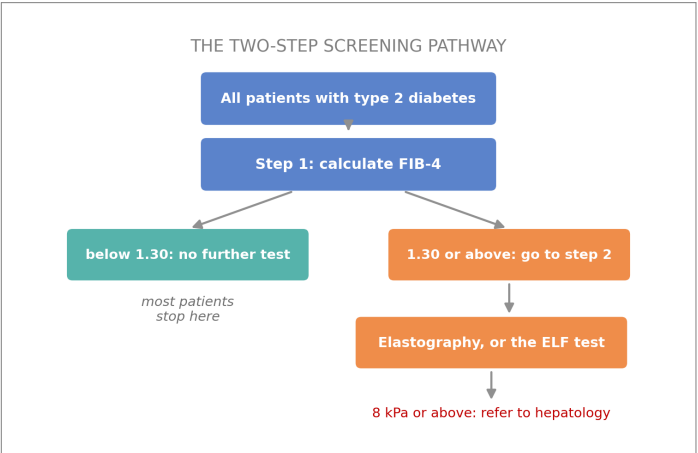


Figure 3: The two-step screening pathway as recommended [8,9,12]

Step	Test	Action
Step 1	FIB-4 below 1.30	Advanced fibrosis unlikely; no further test
Step 1	FIB-4 1.30 or above	Proceed to second-line assessment
Step 2	Liver stiffness below 8 kPa	Advanced fibrosis unlikely
Step 2	Liver stiffness 8 kPa or above	Refer to hepatology
Step 2	Liver stiffness 15 kPa or above	High probability of advanced disease

Table 1: The stepwise non-invasive pathway and the action attached to each result [8,9,12]

What elastography detects: A cross-sectional study of 149 people with type 2 diabetes and steatotic liver disease used transient elastography as the reference. Advanced fibrosis was present in 7.4 per cent (95% CI 3.7 to 12.8), while some degree of fibrosis was detected in 75.8 per cent (95% CI 68.2 to 82.5) (Figure 6) [13]. The gap between those two figures is worth holding on to: most of these patients have measurable fibrosis and very few have the amount that carries prognostic weight.

Table 2: Principal studies reviewed, with the finding as reported by the original investigators

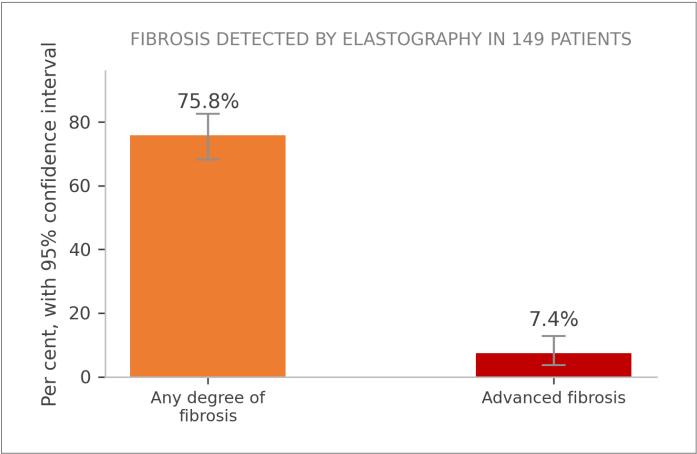


Figure 6: Fibrosis detected by elastography in 149 patients with type 2 diabetes [13]

The scores disagree with each other: In that same cohort, four non-invasive scores were applied to the same patients. The BARD score classified 14.1 per cent as high risk, the NAFLD fibrosis score placed 8.7 per cent in the F3 to F4 range, FIB-4 identified 5.4 per cent as high risk and APRI 3.4 per cent as having severe fibrosis (Figure 1) [13]. Against an elastography-defined prevalence of 7.4 per cent, the four scores bracket the answer without agreeing on it, and a patient's classification depends materially on which score the clinic uses.

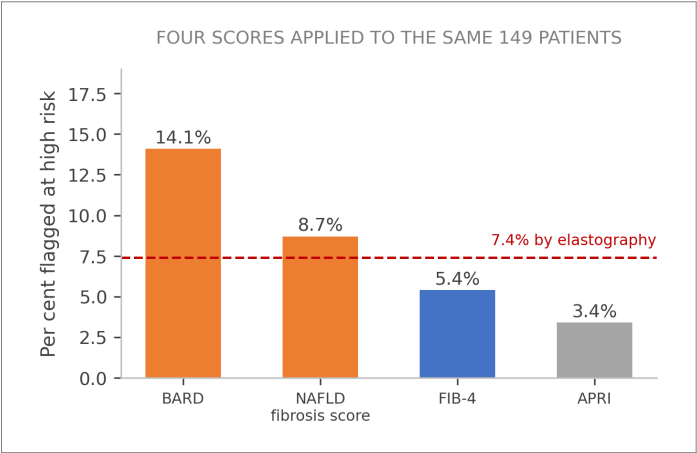


Figure 1: Four non-invasive scores applied to the same 149 patients [13]

How FIB-4 performs in diabetes: Reported discrimination is modest. In a cohort of 1,503 individuals, a modified index developed specifically for diabetes achieved an area under the curve of 0.771 against 0.735 for FIB-4 ($p = 0.012$) [14]. In 273 patients with type 2 diabetes, an elastography-based index combining liver stiffness with transaminase and steatosis measurement reached 0.936 against 0.711 for FIB-4 (Figure 4) [15]. FIB-4 was derived in populations with viral hepatitis rather than diabetes, and its dependence on age causes systematic misclassification at the extremes of the age range, which has prompted proposals for age-adapted thresholds [16,17]. Individual patient data meta-analysis and trial baseline datasets give a broader view of how these tests compare [23,24], and sequential combinations have been proposed to improve on any

single score [26,33,34].

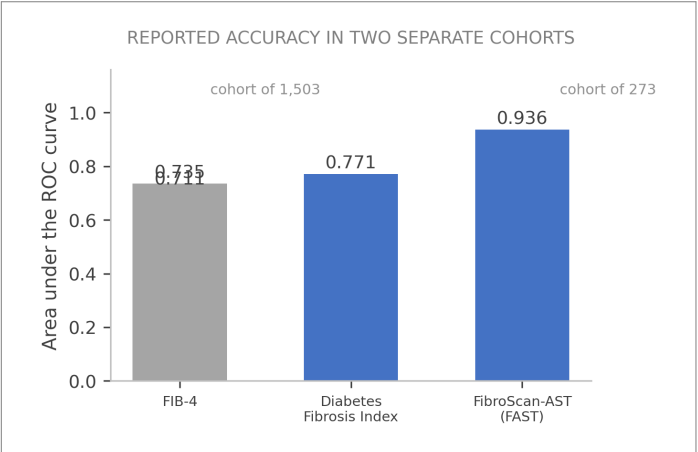


Figure 4: Reported accuracy of FIB-4 against alternative indices in two cohorts [14,15]

Study	Population and reference	Principal reported finding
Primary care cohort [11]	308 with type 2 diabetes, elastography	59% steatotic liver disease; 7% suspected advanced fibrosis
Cross-sectional cohort [13]	149 with diabetes and steatosis, elastography	Advanced fibrosis 7.4%; any fibrosis 75.8%
Same cohort [13]	Four scores, same patients	High risk in 14.1%, 8.7%, 5.4% and 3.4%
Modified index study [14]	1,503 individuals	Diabetes-specific index 0.771 against FIB-4 0.735
Elastography index study [15]	273 with type 2 diabetes	Combined index 0.936 against FIB-4 0.711
Society guidance [8,9,10]	Consensus recommendations	Two-step pathway from FIB-4 to elastography or ELF

Where the guidelines disagree: The recommendations are not identical. There is an unresolved discrepancy over whether every patient with a FIB-4 above 1.30 should undergo second-line assessment, or only those in the intermediate band between 1.30 and 2.66, with values above that referred directly [8,10,18]. The practical consequence is the size of the group sent for elastography, which in a condition affecting most people with diabetes is the difference between a feasible pathway and an unaffordable one [19,20].

Point of difference	Position taken	Consequence
Threshold for step 2	Any FIB-4 above 1.30	Larger group tested; higher cost
Threshold for step 2	Only 1.30 to 2.66	Smaller group; direct referral above 2.66
Age adjustment	Fixed 1.30 threshold	Misclassification in older patients
Age adjustment	Age-adapted thresholds	Fewer false positives above 65

Table 3: Unresolved points in the recommended pathway and their practical effect [8,10,16,18]

What fibrosis stage predicts: The reason staging matters is that outcome tracks fibrosis and not the other histological features. Long-term follow-up of biopsied cohorts found fibrosis stage to be the strongest predictor of disease-specific mortality, and meta-analysis across studies showed mortality rising with each stage [6,27,28]. Prospective outcome data confirm that patients with advanced fibrosis accumulate liver-related events

at a rate that those without do not [7]. This is why a pathway that stops at detecting steatosis achieves very little, and why the second step of the pathway carries the clinical weight.

Combining tests rather than choosing between them: Because no single non-invasive test performs well enough alone, sequential combinations have been proposed, applying a second test only to those whose first result is indeterminate [26,33]. Individual patient data meta-analysis across cohorts has compared the available tests directly and supports the general approach while showing that accuracy in unselected populations is lower than in the enriched cohorts where these tests were derived [23,24]. Published care pathways translate this into a sequence that primary care can follow [25,32].

Discussion

The case for screening is not in dispute. Liver disease in diabetes is common, asymptomatic until late, and the group with advanced fibrosis carries a materially worse prognosis that current management does not address unless it is identified [6,7,11]. A pathway that starts with a score calculable from tests already in the record is a reasonable way to begin.

What deserves more scepticism is the confidence placed in the first step. Four validated scores applied to one group of 149 patients returned 14.1, 8.7, 5.4 and 3.4 per cent [13]. That is a fourfold spread, and it means a statement that a given proportion of patients has advanced fibrosis is incomplete without naming the instrument. FIB-4 sat second-lowest in that comparison and its reported discrimination in diabetes cohorts, 0.711 and 0.735, is modest for a test used to close the pathway for the majority of patients [14,15].

The reason is structural. FIB-4 was derived in populations with viral hepatitis, where the relationship between transaminases, platelets and fibrosis differs from that in metabolic liver disease, and it incorporates age directly, so an older patient with no liver disease can cross the threshold on age alone [16,17]. Applying it to a diabetes population is an extrapolation, and the diabetes-specific index that outperformed it, at 0.771 against 0.735, did so by only a modest margin [14].

The 75.8 per cent figure is the one most likely to be misread. Some degree of fibrosis in three quarters of patients sounds alarming, and it is not the same finding as advanced fibrosis in 7.4 per cent [13]. Mild fibrosis is common, frequently non-progressive, and does not by itself warrant referral. Reporting the higher number without the lower one would generate referrals the hepatology service cannot absorb and anxiety the evidence does not support.

On the guideline disagreement, the honest position is that it is unresolved rather than settled in either direction [8,10,18]. Sending everyone above 1.30 for elastography is more sensitive and considerably more expensive; restricting step two to the 1.30 to 2.66 band is cheaper and accepts that some cases will be referred directly on a score alone. Which is preferable depends

on local elastography capacity, which is not evenly distributed and is the practical constraint that most determines whether any of this happens [19,20]. Published care pathways set out how the steps might be organised in practice [25,32].

A further consideration is what happens to the large group in the middle. If three quarters of patients have some fibrosis and one in thirteen has advanced fibrosis, then the majority of positive findings on a sensitive test represent disease that will not progress in that person's lifetime [13,27]. Communicating that distinction is not straightforward. A patient told they have liver fibrosis will reasonably assume it is the kind that matters, and the pathway generates that conversation far more often than it generates a referral.

There is also an unresolved question about what a positive result changes. Screening is worthwhile if identification leads to something, and for advanced fibrosis it does: surveillance, hepatology input and attention to the metabolic drivers [8,9,25]. For the much larger group with mild fibrosis the management is the management of type 2 diabetes and cardiovascular risk, which was already indicated [5,29]. No randomised trial has yet shown that screening for fibrosis in diabetes improves liver-related outcomes, and that gap is worth naming rather than assuming the benefit follows from the association [7,19].

2. Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, et al. "A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement". *J Hepatol* 73(2020):202-209.

Study limitations

The limitations belong to the underlying literature. Most prevalence estimates rest on elastography rather than biopsy, and elastography itself has failure and unreliability rates that rise with obesity, which is common in this population [11,13,21]. The cross-sectional cohort comparing four scores includes 149 patients, so its confidence intervals are wide, and the advanced fibrosis estimate of 7.4 per cent spans 3.7 to 12.8 per cent [13]. Accuracy figures for non-invasive tests are derived in cohorts enriched for disease and will fall in unselected screening populations [14,15]. FIB-4 was developed in viral hepatitis and its thresholds have not been recalibrated for diabetes in routine use [16,17]. Guidelines differ on the referral threshold and no trial has compared the two strategies on patient outcomes [8,10,18]. No randomised evidence shows that screening for fibrosis in diabetes improves liver-related mortality [7,19]. And the studies reviewed here come from a small number of settings with ready access to elastography, which is not the general case [11,20].

Conclusion

Most people with type 2 diabetes have steatotic liver disease and a small minority have the advanced fibrosis that changes their prognosis, which makes a case-finding pathway sensible in principle. The pathway as recommended rests on FIB-4, and FIB-4 is the weakest part of it: derived in a different disease, dependent on age, and reporting areas under the curve of around 0.71 to 0.74 in diabetes cohorts, where alternatives reach higher. Four validated scores applied to the same 149 patients disagreed by a factor of four. None of that argues against screening, and all of it argues for reporting which instrument produced a given number, and for keeping the distinction between any fibrosis at three quarters of patients and advanced fibrosis at one in thirteen firmly in view.

Acknowledgements

The authors thank the investigators whose cohorts and diagnostic comparisons are drawn together in this article, and the primary care teams who offered elastography to unselected patients with diabetes.

Funding

No dedicated funding from public, commercial or charitable sources supported the preparation of this review.

Conflict of Interest

The authors declare no competing interests.

3. Younossi ZM, Golabi P, de Avila L, Paik JM, Srishord M, Fukui N, et al. "The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: a systematic review and meta-analysis". *J Hepatol* 71(2019):793-801.

Ethics Statement

This article reviews previously published studies only. No new patient data were collected and no participants were recruited, so ethical approval was not required.

References

1. Rinella ME, Lazarus JV, Ratziu V, Francque SM, Sanyal AJ, Kanwal F, et al. "A multisociety Delphi consensus statement on new fatty liver disease nomenclature". *Hepatology* 78(2023):1966-1986.
4. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. "Global epidemiology of nonalcoholic fatty liver disease: meta-analytic assessment of prevalence, incidence, and outcomes". *Hepatology* 64(2016):73-84.
5. Targher G, Corey KE, Byrne CD, Roden M. "The complex link between NAFLD and type 2 diabetes mellitus: mechanisms and treatments". *Nat Rev Gastroenterol Hepatol* 18(2021):599-612.
6. Angulo P, Kleiner DE, Dam-Larsen S, Adams LA, Bjornsson ES, Charatcharoenwitthaya P, et al. "Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease". *Gastroenterology* 149(2015):389-397.
7. Sanyal AJ, Van Natta ML, Clark J, Neuschwander-Tetri BA, Diehl A, Dasarathy S, et al. "Prospective study of outcomes in adults with nonalcoholic fatty liver disease". *N Engl J Med* 385(2021):1559-1569.
8. Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, Abdelmalek MF, Caldwell S, Barb D, et al. "AASLD practice guidance on the clinical assessment and management of nonalcoholic fatty liver disease". *Hepatology* 77(2023):1797-1835.
9. European Association for the Study of the Liver. "EASL-EASD-EASO clinical practice guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD)". *J Hepatol* 81(2024):492-542.
10. Cusi K, Isaacs S, Barb D, Basu R, Caprio S, Garvey WT, et al. "American Association of Clinical Endocrinology clinical practice guideline for the diagnosis and management of nonalcoholic fatty liver disease in primary care and endocrinology clinical settings". *Endocr Pract* 28(2022):528-562.
11. Primary care screening investigators. "Prevalence of metabolic dysfunction-associated steatotic liver disease and advanced fibrosis among people with type 2 diabetes in primary care". *Diabetes Obes Metab* (2024).
12. Newsome PN, Sasso M, Deeks JJ, Paredes A, Boursier J, Chan WK, et al. "FibroScan-AST (FAST) score for the non-invasive identification of patients with non-alcoholic steatohepatitis with significant activity and fibrosis: a prospective derivation and global validation study". *Lancet Gastroenterol Hepatol* 5(2020):362-373.
13. Eastern India cohort investigators. "Prevalence of hepatic fibrosis and its predictors in patients with type 2 diabetes mellitus and metabolic dysfunction-associated steatotic liver disease: a cross-sectional study". *J Clin Exp Hepatol* (2025).
14. Modified index investigators. "A modified FIB-4 index for detecting advanced fibrosis in individuals with metabolic dysfunction-associated steatotic liver disease and type 2 diabetes". *Diabetes Res Clin Pract* (2025).
15. Saudi comparison investigators. "Accuracy of FibroScan-AST score and FIB-4 for detecting significant liver fibrosis in patients with type 2 diabetes mellitus". *Saudi J Gastroenterol* (2024).
16. McPherson S, Hardy T, Dufour JF, Petta S, Romero-Gomez M, Allison M, et al. "Age as a confounding factor for the accurate non-invasive diagnosis of advanced NAFLD fibrosis". *Am J Gastroenterol* 112(2017):740-751.
17. Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, et al. "Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection". *Hepatology* 43(2006):1317-1325.

18. Two-step pathway investigators. "Two-step strategy for identifying advanced fibrosis and liver-related events in metabolic dysfunction-associated steatotic liver disease". *Clin Mol Hepatol* (2025).
19. Srivastava A, Gailer R, Tanwar S, Trembling P, Parkes J, Rodger A, et al. "Prospective evaluation of a primary care referral pathway for patients with non-alcoholic fatty liver disease". *J Hepatol* 71(2019):371-378.
20. Tsochatzis EA, Newsome PN. "Non-alcoholic fatty liver disease and the interface between primary and secondary care". *Lancet Gastroenterol Hepatol* 3(2018):509-517.
21. Eddowes PJ, Sasso M, Allison M, Tsochatzis E, Anstee QM, Sheridan D, et al. "Accuracy of FibroScan controlled attenuation parameter and liver stiffness measurement in assessing steatosis and fibrosis in patients with nonalcoholic fatty liver disease". *Gastroenterology* 156(2019):1717-1730.
22. Vali Y, Lee J, Boursier J, Spijker R, Loffler J, Verheij J, et al. "Enhanced liver fibrosis test for the non-invasive diagnosis of fibrosis in patients with NAFLD: a systematic review and meta-analysis". *J Hepatol* 73(2020):252-262.
23. Mozes FE, Lee JA, Selvaraj EA, Jayaswal ANA, Trauner M, Boursier J, et al. "Diagnostic accuracy of non-invasive tests for advanced fibrosis in patients with NAFLD: an individual patient data meta-analysis". *Gut* 71(2022):1006-1019.
24. Anstee QM, Lawitz EJ, Alkhouri N, Wong VW, Romero-Gomez M, Okanoue T, et al. "Noninvasive tests accurately identify advanced fibrosis due to NASH: baseline data from the STELLAR trials". *Hepatology* 70(2019):1521-1530.
25. Kanwal F, Shubrook JH, Adams LA, Pfothenauer K, Wai-Sun Wong V, Wright E, et al. "Clinical care pathway for the risk stratification and management of patients with nonalcoholic fatty liver disease". *Gastroenterology* 161(2021):1657-1669.
26. Boursier J, Guillaume M, Leroy V, Irles M, Roux M, Lannes A, et al. "New sequential combinations of non-invasive fibrosis tests provide an accurate diagnosis of advanced fibrosis in NAFLD". *J Hepatol* 71(2019):389-396.
27. Ekstedt M, Hagstrom H, Nasr P, Fredrikson M, Stal P, Kechagias S, et al. "Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up". *Hepatology* 61(2015):1547-1554.
28. Dulai PS, Singh S, Patel J, Soni M, Prokop LJ, Younossi Z, et al. "Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: systematic review and meta-analysis". *Hepatology* 65(2017):1557-1565.
29. Bril F, Cusi K. "Management of nonalcoholic fatty liver disease in patients with type 2 diabetes: a call to action". *Diabetes Care* 40(2017):419-430.
30. Lomonaco R, Godinez Leiva E, Bril F, Shrestha S, Mansour L, Budd J, et al. "Advanced liver fibrosis is common in patients with type 2 diabetes followed in the outpatient setting: the need for systematic screening". *Diabetes Care* 44(2021):399-406.
31. Ajmera V, Cepin S, Tesfai K, Hofflich H, Cadman K, Lopez S, et al. "A prospective study on the prevalence of NAFLD, advanced fibrosis, cirrhosis and hepatocellular carcinoma in people with type 2 diabetes". *J Hepatol* 78(2023):471-478.
32. Castera L, Friedrich-Rust M, Loomba R. "Noninvasive assessment of liver disease in patients with nonalcoholic fatty liver disease". *Gastroenterology* 156(2019):1264-1281.
33. Shah AG, Lydecker A, Murray K, Tetri BN, Contos MJ, Sanyal AJ. "Comparison of noninvasive markers of fibrosis in patients with nonalcoholic fatty liver disease". *Clin Gastroenterol Hepatol* 7(2009):1104-1112.
34. Harrison SA, Oliver D, Arnold HL, Gogia S, Neuschwander-Tetri BA. "Development and validation of a simple NAFLD clinical scoring system for identifying patients without advanced disease". *Gut* 57(2008):1441-1447.

Citation: Carrara D, Zumbrunn N, Torok G. "Metabolic Dysfunction-Associated Steatotic Liver Disease in Type 2 Diabetes: A Narrative Review of Who Needs Fibrosis Staging and When". DOI: 10.5281/zenodo.22258263