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Management of NAFLD patients with advanced fibrosis

Douglas Maya-Miles[1,2,3] | Javier Ampuero[1,2,3,4] | Rocío Gallego-Durán[1,2,3] | Paola Dingianna[2] | Manuel Romero-Gómez[1,2,3,4]

[1]Institute of Biomedicine of Seville (IBiS), SeLiver Group, Virgen del Rocío University Hospital/CSIC/University of Seville, Seville, Spain

[2]UCM Digestive Diseases, Virgen del Rocío University Hospital, Seville, Spain

[3]CIBER Hepatic and Digestive Diseases (CIBERehd), Seville, Spain

[4]University of Seville, Seville, Spain

Correspondence
Prof. Manuel Romero-Gómez, MD, PhD, UCM Digestive Diseases, Avda. Manuel Siurot s/n, ZIP Code 41013, Sevilla, Spain.
Email: mromerogomez@us.es

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Abstract

The prevalence of non alcoholic fatty liver disease (NAFLD) has increased to 25% in the general population and could double by 2030. Liver fibrosis is the main indicator of morbidity and mortality and recent estimations suggest a substantial number of individuals with undiagnosed advanced liver disease. Strategies to monitor advanced fibrosis are essential for early detection, referral, diagnosis and treatment in primary care and endocrine units, where NAFLD and consequently liver fibrosis are more prevalent. Blood-based non-invasive methods could be used to stratify patients according to the risk of the progression of fibrosis and combined with imaging techniques to improve stratification. Powerful new diagnostic tools such as MRE and PDFF are emerging and might prevent the need for liver biopsy in the near future. The current therapeutic landscape of NAFLD is rapidly evolving with an increasing number of molecules that treat key factors involved in its progression, but that still have a limited or no ability to effectively reverse fibrosis. Management of this disease will probably require a combination of sequential and personalized treatments as a result of its complex and dynamic pathophysiology. Lifestyle interventions are still the most effective therapeutic option and should be better integrated into patient management together with specific programs of bariatric endoscopy/surgery for morbidly obese patients.

KEYWORDS

advanced liver disease, liver fibrosis, NAFLD, NASH, screening

Key points

- Strategies to identify and treat patients with or at risk of advanced fibrosis as a result of NAFLD must be given priority.

Abbreviations: ADAPT, Age, presence of DiAbetes, PRO-C3 and plaTelet count; ALT, Alanine transaminase; APRI, AST-to-Platelet Ratio Index; AST, Aspartate transaminase; BMI, Body mass Index; CI, Confidence Interval; CPA, Collagen Proportionate Area; CVD, Cardiovascular disease; ECM, Extracellular Collagen Matrix; ELF, Enhanced Liver Fibrosis; FIB-4, Fibrosis Score-4; FXR, Farnesoid X receptor; HFS, Hepamet Fibrosis Score; HOMA, Homeostatic Model Assessment for Insulin Resistance; IQR, Interquartile range; MRE, Magnetic Resonance Elastography; NAFLD, Non-Alcoholic Fatty Liver Disease; NASH, Non-Alcoholic SteatoHepatitis; NASH-CRN, NASH Clinical Research Network; NFS, NAFLD Fibrosis Score; NITs, Non-invasive Tests; NPV, Negative Predictive Values; p-2D-3D SWE, (point-2D-3D) Shear Wave Elastography; PPAR, Peroxisome Proliferator Activated Receptor; PPV, Positive Predictive Values; PRO-C3, N-terminal type III Collagen Propeptide; TD2M, Type II Diabetes Mellitus; TE (VCTE), (Vibration controlled) Transient Elastography.

- Composite scores for the assessment of fibrosis are easy-to-use tools that help identifying patients with minimal or advanced fibrosis, and should be implemented in primary care health centres and endocrine units.
- Patient management should focus on treating comorbidities and risk factors that are more likely to worsen fibrosis and include active and well-designed standardized lifestyle interventions.

1 | INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is known to be the most prevalent chronic liver disease worldwide. The estimated pooled prevalence in the general population is 25% for NAFLD and ranges from 3% to 5% for non-alcoholic steatohepatitis (NASH) with wide geographical variations across the world. NAFLD has traditionally been described as a group of nosological entities characterized by a high accumulation of fat in the liver cells (steatosis) in the absence of any other cause of liver disease, alcohol consumption or steatogenic drug use. However, the last decade has provided ample evidence of a complex interplay between NAFLD and many other diseases, especially type 2 diabetes mellitus (T2DM) and obesity, with a prevalence of 55.5% which can reach up to 90% in extremely obese patients.[1] NAFLD alone is a risk factor for cardiovascular disease, the most common cause of death in these patients. NAFLD has also been associated with the development of numerous diseases including extrahepatic malignancies, chronic kidney disease, certain endocrinopathies including polycystic ovary syndrome and osteoporosis, brain aging and cognitive impairment.[2]

The spectrum of NAFLD ranges from simple steatosis, a relatively benign form of the disease, to NASH, which may or may not be associated with liver fibrosis. NASH and fibrosis seem to promote the development of diabetes mellitus, dyslipidaemia and arterial hypertension in patients without baseline metabolic disturbances.[3] Because of the strong association of this disease with general metabolic disorders as well as the coexistence of metabolic risk factors with some level of alcohol consumption in a substantial proportion of the population, alternative names have recently been proposed for this disease such as metabolic associated fatty liver disease (MAFLD) or dysmetabolism-associated fatty liver disease (DAFLD).[4,5] Whatever term best defines or classifies this disease,[6] it is clear that the global increase in obesity and dysmetabolic disorders together with an ageing population makes NAFLD a serious public health problem.

Chronic injury from NAFLD inhibits the regenerative capacity of the liver because of a state of overnutrition that generates an imbalance in the hepatic lipid metabolism that promotes cellular stress, apoptosis and liver injury. In these cases, fibrosis is a result of a complex crosstalk among different organs and also among most of the different cell types in the liver, in particular hepatic stellate cells (HSCs) and immune cells, which are the key drivers of fibrosis. Diet-induced accumulation of lipid overload and intrahepatic insulin resistance are considered to be key factors that trigger NASH through persistent accumulation of lipotoxic and glucotoxic damage, which mainly takes place in hepatocytes. Lipotoxicity and glucotoxicity eventually trigger apoptosis and liver injury along with a production of pro-inflammatory cytokines, chemokines and damage-associated molecular patterns (DAMPs) which upregulate the activation of Kupffer cells and monocyte-derived macrophages. This activation further promotes the transdifferentiation of hepatic stellate cells into myofibroblasts. In the long run, dendritic cells activate CD4 + T cells, which polarize Th1 and Th17 into pro-inflammatory lymphocytes worsening liver damage and inflammation.

Hepatic fibrosis is an adaptive mechanism whose main goal is to repair damaged tissue and is characterized by an accumulation of extracellular matrix (ECM). If the insult persists chronic liver injury may lead to cirrhosis, which is characterized by a distortion of the hepatic architecture generating abnormal blood flow and, in certain cases, portal hypertension, the major cause of clinical complications, including hydropic decompensation, bleeding events and hepatic encephalopathy. Liver fibrosis also progressively restricts normal liver regeneration increasing the risk of liver failure, and generates a favourable micro-environment for the development of liver cancer through mechanisms that have not been completely clarified.[7]

Although the prevalence of NAFLD is high, not all patients are at risk of developing severe complications. In 2017, one meta-analysis including 1,495 NAFLD patients evaluating the risk of all-cause mortality and liver-related mortality reported a linear increase in all-cause mortality as fibrosis progresses and a more sudden increase in liver-related mortality after stage 2.[8] A more recent meta-analysis including 4,428 biopsy-proven NAFLD patients reached a similar conclusion. It is important to note that this study did not find evidence of an additional risk of NASH compared to patients with simple steatosis or NASH and the same stage of fibrosis.[9] A nationwide longitudinal study evaluating 11,154 participants for a median follow-up of 14.5 years with 1795 registered deaths concluded that NAFLD per se was not associated with higher mortality [1.05; 95% confidence interval [CI]: 0.93-1.19]. On the other hand, high APRI (>1.5), NFS (>0.676) and FIB-4 (>2.67) values, three non-invasive scores to determine the risk of advanced fibrosis, were associated with mortality even after adjustment for other known predictors (NFS: hazard ratio, 1.69; 95% CI, 1.09-2.63; APRI: hazard ratio, 1.85; 95% CI, 1.02-3.37; FIB-4: hazard ratio, 1.66; 95% CI, 0.98-2.82).[10] Overall, these data suggest that although NASH plays a key role in driving and/or accelerating the progression of fibrosis in patients with NAFLD, liver fibrosis is probably the most important factor to be taken into account when evaluating patient prognosis.

1.1 | Screening advanced liver disease in the general population

Liver biopsy is still the reference method for the diagnosis of NAFLD. It determines the grade of steatosis, necroinflammation and fibrosis simultaneously and is still the only available technique to effectively diagnose NASH. The staging of fibrosis is usually based on the NASH-CRN score, which uses the Kleiner score to classify fibrosis, with moderate accuracy for intermediate stages because of a variability in inter- and intra-observer agreement of almost 25% for overlapping stages of fibrosis.[11] Several alternative methods have been developed to provide more objective quantification of fibrosis. Morphometry provides a finite-quantitative scale of the amounts of collagen, the Collagen Proportionate Area (CPA), which has already been used in certain clinical trials for Hepatitis C but it is time consuming and has a non-linear relationship with the stage of fibrosis.[12] Q-fibrosis, a technique that has been shown to improve the underestimation of staging in suboptimal biopsies (<15 mm) and under- and over-scoring by different pathologists ($P < .001$), has recently been modified and applied to NAFLD to improve the discrimination between F1 and F2 patients.[13] Liver biopsy is still the best method to evaluate the progression and regression of fibrosis but it is limited by cost, accuracy, a risk of adverse events and invasiveness so that it is unsuitable for large-scale screening.

Non-invasive techniques (NITs) provide a continuous measurement estimated by the integration of different sets of biological and/or physical properties in a dynamic algorithm. These algorithms usually integrate anthropometric parameters and the levels of certain components, which can be quantified in serum or blood samples. NITs can also be based on a subset of imaging techniques, which are usually performed to help estimating liver fat content and/or liver stiffness, an intrinsic physical property of the liver parenchyma. Serum biomarkers range from simple, inexpensive tests such as the AST-to- Platelet ratio Index (APRI), Fibrosis-4 (FIB-4), NAFLD fibrosis score (NFS) or Hepamet Fibrosis Score (HFS) to more sophisticated and patented tests such as the FibroTest®, Fibrometer®, ELF, Hepascore and PRO-C3. Several potential new NITs are currently being investigated and use various combinations of cytokines, chemokines, genetic polymorphisms, microRNAs and post-translational modified glycoproteins to assess fibrosis. Imaging techniques include vibration-controlled transient elastography (VCTE or Fibroscan) and magnetic resonance elastography (MRE), which use mechanical drivers to generate shear wave and measure its velocity using sonographic Doppler or MR techniques, and shear wave elastography (pSWE 2D-SWE, 3D-SWE), which uses high frequency ultrasound impulses for shear wave generation from one or multiple frequencies in real-time using ultrasound. These methods are usually accurate enough to exclude the presence of advanced liver disease, but not to effectively classify a significant number of patients that remain in the grey zone. None of them has proven so far a robust ability to dynamically monitor disease progression over time.

The ability of NITs to rule in or rule out liver fibrosis varies significantly depending on the cut-off value, which can be modified depending on the desired endpoint. Current available NITs have usually low to moderate positive predictive values and, therefore, a limited ability to confirm significant and advanced fibrosis, which often requires additional clinical information for a clear diagnosis. In contrast, the negative predictive value (NPV) of NITs is generally strong, allowing the clinician to confidently exclude advanced fibrosis or cirrhosis. The estimated prevalence of advanced fibrosis and cirrhosis in the population being studied, as well as certain comorbidities (diabetes, obesity, age), can influence the results of NITs for the diagnosis of advanced fibrosis. Differences in ethnicity can also influence certain NITs such as FIB-4 and NFS, whose results have been shown to be less reliable in South Asians than in Caucasians. All of these factors should be taken into consideration in the study design as well as the conclusions.[14] Table 1 summarizes the ability of several NITs to predict significant and advanced fibrosis according to four recent metanalyses.[15-18]

None of the existing NITs provides an analysis of fibrosis comparable to liver biopsy. However, NITs can be used to identify high-risk patients in the global population. Implementing targeted diagnostic screening programs in primary care and outpatient clinics could greatly reduce the number of patients with undiagnosed advanced liver fibrosis, which could represent 6-7% of the population.[19] Screening should be performed in patients with obesity, diabetes or individual components of the metabolic syndrome as well as in those with increased liver enzymes or steatosis. It is important to note that abnormal liver blood enzymes are not specific for the diagnosis or exclusion of fibrosis, so they must be incorporated into algorithms or associated with other tools to assess the extent of fibrosis.

Most of the algorithms and screening protocols proposed combine a two-stage evaluation. First, a non-invasive test with a single cut-off is performed in primary care or endocrinology units to exclude patients with a low risk of advanced fibrosis. FIB-4 or NFS are inexpensive, easy-to-perform tests with good NPV for the exclusion of advanced fibrosis using a single cut off (NFS<−1.455 and FIB4 < 1.3), and can be used as a first screening option for intermediate-to-high–risk patients. Both these tests may be influenced by age and should use a different cut-off for patients aged > 65 (NFS < 0.12 and FIB-4 < 2.0). FIB4 is easier to perform in primary care than NFS because the latter also requires albumin. Patients with available HOMA-IR scores can also be assessed for advanced fibrosis using a single cut off with the Hepamet Fibrosis Score (HFS < 0.12). HFS has been shown to be better than NFS and FIB-4 for the exclusion of advanced fibrosis, to significantly reduce the grey zone and seems to be less influenced by BMI and ALT levels. This test also improves classification of non-diabetic patients probably because the formula includes the HOMA index (https://www.hepamet-fibrosis-score.eu/) (Figure 1A).[20]

When advanced fibrosis cannot be excluded, patients should then undergo transient elastography. The cut-off for advanced fibrosis with TE is confirmed with 8 or 6.2 kPa (M and XL probes, respectively) for the exclusion of advanced fibrosis. The XL probe

TABLE 1 Summary of sensitivity, specificity and AUC values to identify significant (≥F2) and advanced fibrosis (≥F3). AUC: Area under the curve; SUM: Summary; Rest of acronyms and abbreviations are included in the abbreviations list

		SIGNIFICANT FIBROSIS (F ≥ 2)					ADVANCED FIBROSIS (F ≥ 3)				
Xiao et al 2017[15]	APRI	4 (864)	0.43-1.5	59.3 (33.3-71.1)	77.1 (66.2-90.6)	11 (2352) 0.70 [0.64-0.76] (0.54-0.87)	5 (729) 7 (1,351) 4 (1101) 4 (682)	0.452-0.50 0.54-0.98 1.00 1.50	72.9 (50.0-87.4) 68.6 (61.0-76.2) 43.2 (27.0-67.0) 32.9 (6.3-70.0)	67.7 (43.1-91.0) 72.7 (59.4-86.0) 86.1 (81.0-89.0) 90.5 (74.5-97.0)	29 (6746) 0.75 [0.72-0.77] (0.60-0.92)
	BARD	1 (242)	2	44.3	70.4	5 (1330) 0.64 [0.53-0.75] (0.50-0.73)	1 (242) 14 (3057) 5 (736)	1.5 2 3-4	83.0 75.2 (41.7-100) 59.4 (33.3-85.2)	59.0 61.6 (32.5-88.9) 75.1 (59.9-91.8)	30 (7791) 0.73 [0.71-0.75] (0.64-0.87)
	FIB-4	4 (819)	0.37-3.25	64.4 (54.4-77.8)	70.0 (60.0-87.5)	12 (2330) 0.75 [0.70-0.79] (0.59-0.84)	10 (2759) 8 (1533) 6 (1910) 6 (1890) 4 (543)	1.24-1.45 1.51-2.24 2.67 3.25 5.31-10.62	77.8 (63.0-90.0) 77.0 (70.6-89.5) 31.9 (12.0-63.2) 37.3 (5.0-56.0) 67.5 (50.0-100)	71.2 (55.5-88.0) 79.2 (67.1-93.6) 95.7 (88.3-98.7) 95.8 (89.0-100) 80.8 (54.0-100)	34 (8245) 0.80 [0.77-0.84] (0.37-0.95)
	NFS	2 (432)	-1.1	65.5 (60.9-70.1)	82.5 (68.7-96.3)	11 (2098) 0.72 [0.65-0.79] (0.55-0.88)	2 (106) 10 (3057) 5 (963) 14 (3896) 1 (235)	[−26.93]-[−2.16] -1.455 [−1.31]-[0.156] 0.67-0.676 0.735	80.5 (78.0-83.0) 72.9 (22.7-96.0) 78.2 (69.0-86.4) 43.1 (8.3-100) 68.4	69.5 (69.0-70.0) 73.8 (42.9-100) 71.7 (60.0-83.0) 88.4 (25.0-100) 88.3	38 (9245) 0.78 [0.75-0.81] (0.52-0.96)
	TE (M probe)	3 (559) 10 (1496) 8 (1110)	5.8 6.65-7 7.25-11	91.7 (90.0-94.0) 74.1 (58.8-100) 65.7 (52.5-84.0)	57.4 (42.0-80.0) 68.6 (44.7-84.3) 84.5 (70.0-93.2)	15 (2207) 0.83 [0.79-0.86] (0.67-1.00)	3 (393) 9 (1540) 5 (1157) 5 (773)	6.95-7.25 7.6-8 8.7-9 9.6-11.4	69.2 (66.7-70.4) 88.9 (65.0-100) 83.3 (76.0-88.4) 80.1 (69.0-100)	66.3 (64.5-67.7) 77.2 (65.9-90.2) 78.0 (62.9-88.0) 89.9 (83.8-96.9)	16 (2495) 0.87 [0.83-0.90] (0.75-0.98)
	TE (XL probe)	4 (654)	4.8-8.2	75.8 (57.0-92.0)	64.8 (37.0-90.0)	3 (318) 0.82 [0.75-0.89] (0.80-0.85)	3 (579)	5.7-9.3	75.3 (57.0-91.0)	74.0 (54.0-90.0)	3 (318) 0.86 [0.78-0.94] (0.84-0.90)
	SWE (pSWE-2d-SWE)	2 (233)	2.67-9.4	85.0 (84.0-86.0)	94.4 (88.9-100)	2 (233) 0.89 [0.46-1.00] (0.85-0.92)	3 (429)	3.02-10.6	89.9 (88.2-91.5)	91.8 (90.0-94.0)	3 (429) 0.91 [0.82-1.00] (0.88-0.95)
	MRE	3 (384)	3.4-3.62	73.2 (65.7-87.3)	90.7 (85.0-95.7)	3 (384) 0.88 [0.83-0.92] (0.86-0.89)	5 (628)	3.62-4.8	85.7 (74.5-92.2)	90.8 (86.9-93.3)	5 (628) 0.93 [0.90-0.97] (0.89-0.96)

(Continues)

TABLE 1 (Continued)

		SIGNIFICANT FIBROSIS (F ≥ 2)					ADVANCED FIBROSIS (F ≥ 3)				
Vali et al 2020[16]	ELF	5 (550)	7.70 9.80 10.51	97 (88-99) 57(40-73) 35 (22-50)	10 (03-26) 89(73-96) 97 (89-99)	5 (550) 0.81 (0.66-0.89) -	11 (4452)	7.70 9.80 10.51	93 (82-98) 65 (49-77) 51 (0.31-0.70)	34 (13-65) 86(77-92) 93 (85-96)	11 (4452) 0.83 (0.71-0.90) -
Jiang et al 2018[17]	TE M or XL probe	10 (?)	6.7-11.0	77 (70-84)	80 (74-84)	10 (?) 0.85 [0.82-0.88] -	11 (1753)	8.0-12.5	79 (69-87)	89 (84-92)	11 (1753) 0.92 [0.89-0.94] -
	SWE	6 (733)	1.16-1.32	70 (59-79)	84 (79-88)	6 (733) 0.86 [0.83-0.89] -	9 (982)	1.34-1.77	89 (73-96)	88 (82-92)	9 (982) 0.94 [0.91-0.95] -
Liang et al 2020[18]	MRE	12 (910)	3.4-3.62	87 (74-97)	86 (71-94)	12 (910) 0.93 [0.90-0.95] -	12 (910)	3.62-4.8	89 (81-94)	84 (63-94)	12 (910) 0.93 [0.90-0.95] -

(A)

	FORMULA/METHODS	ADVANTAGES	LIMITATIONS
FIB-4	age (yr) x AST [U/L]/(platelets [10^9/L] x (ALT [U/L])1/2	1.Cost effective 2. Easy to use and to implement in outpatient clinics and primary care 3. High negative predictive value for advanced fibrosis	1. Low positive predictive value. 2. High percentage in the grey zone. 3. Sensitive to obesity, age, AST and TD2M.
NFS	(-1.675 + 0.037 x age (yr) + 0.094 x BMI (kg/m2) + 1.13 x IFG/diabetes (yes = 1, no = 0) + 0.99 x AST/ALT ratio - 0.013 x platelet count (x10^9/L) - 0.66 x albumin [g/dl])		
HFS	1 / (1 + e[5.390–0.986 × age[45–64 years] − 1.719 × age [≥ 65 years] + 0.875 × male sex − 0.896 × AST[35–69 UI/L] − 2.126 × AST[≥ 70 UI/L] − 0.027 × albumin[4–4.49 g/dL] − 0.897 × albumin[< 4 g/dL] − 0.899 × HOMA [2–3.99 with no T2D] − 1.497 × HOMA [≥ 4 with noT2D] − 2.184 × T2D − 0.882 × platelets[155–219 × 1.000/μL] − 2.233 × platelets [< 155 × 1.000/μL])	1.Cost effective 2. Easy to use and to implement in outpatient clinics and primary care 3. High negative predictive value for advanced fibrosis 4.Less sensitive to obesity, AST and TD2M 5. Not sensitive to age	1. Low positive predictive value. 2. High percentage in the grey zone. 3. Assesment in non-diabetics requires HOMA-IR
TE	TE should be performed by an experienced operator (>100 examinations) following a standardized protocol with the patient, fasting for at least 2 hours, in the supine position, right arm in full abduction, on the midaxillary line with the probe-tip placed in the 9th to 11th intercostal space with a minimum of 10 shots with > 60% valid measurementes (IQR <0.3).	1. Higher diagnostic accuracy than most blood based NITs 2. Best validated imaging technique	1. Less available and/or more costly than NITs 2. Lack of parenchymal assessment 3. Sensitive to ascites, morbid obesity, cholestasis, inflammation from acute hepatitis, and heart failure 4. Operator and experience dependency
MRE	MRE generates mechanical waves generated in a drum device over the liver are imaged for about 15 seconds provides a color-coded liver stiffness map. Use should only be considered if the evaluation with TE is inconclusiv or for research purposes.	1. Highest diagnostic accuracy 2. Not influenced by BMI severe steatosis & hemochromatosis	1. Cost and availability 2. Limited experience & validation 3. Influenced by implanted metallic devices, claustrophobia and iron overload.

(B)

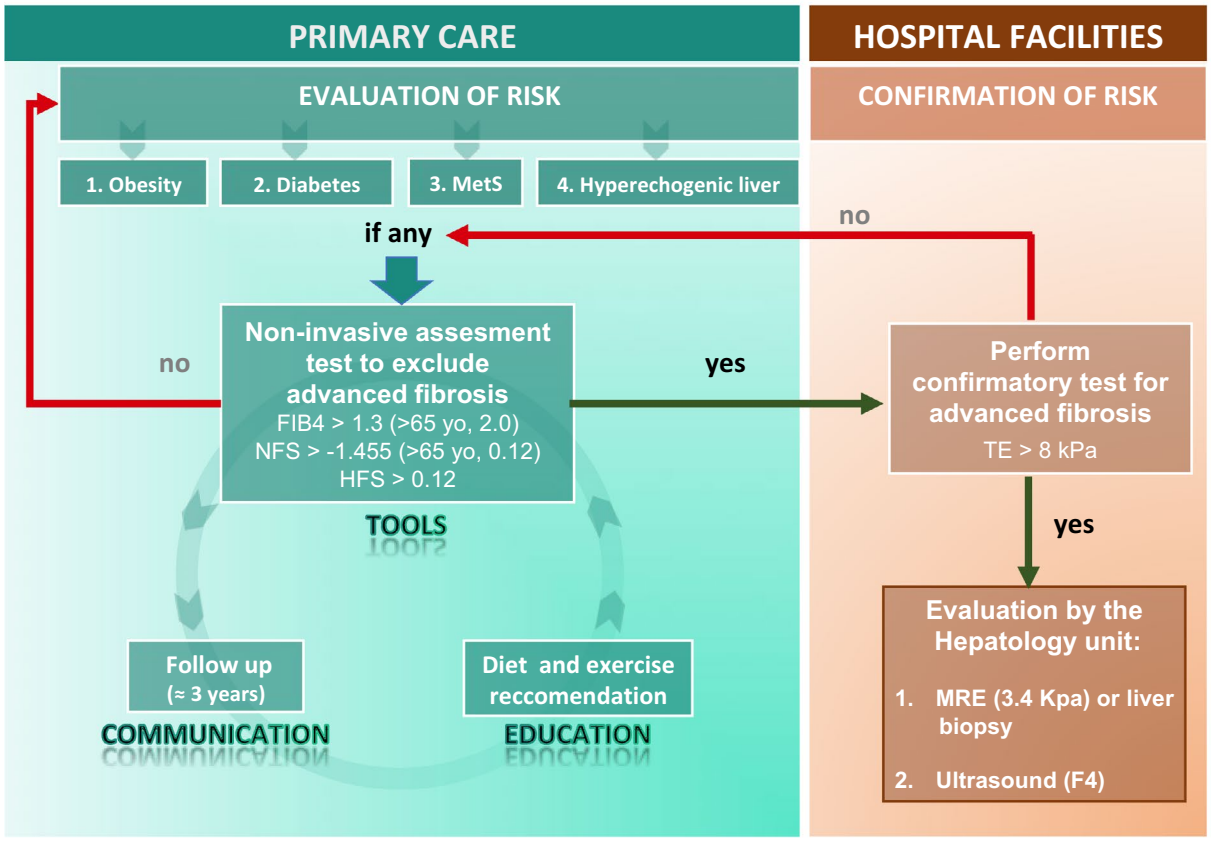

FIGURE 1 Referral care pathway proposed to improve the detection of advanced fibrosis in primary care or non-specialized units. (A) Methods, advantages and disadvantages of NITs proposed in the algorithm. (B) Referral care pathway including cut-off scores. Acronyms and abbreviations are included in the abbreviations list.

is highly recommended in obese patients. Advanced fibrosis can also be assessed using improved non-invasive blood panels such as PRO-C3/ADAPT and ELF (<7.7), or alternative imaging techniques such as MRE (3.4 kPa) ir 2D-SWE (8 kPa). Iron-overload can significantly influence MRE results and should be assessed with other sequences.[16,17] Patients above the recommended thresholds should be referred to a hepatologist for a possible liver biopsy to confirm the diagnosis, or ultrasound to confirm cirrhosis. Patients below the threshold should be followed in primary care using serum-based NITs if there are no other clinical symptoms suggesting advanced liver disease (2-3 years) (Figure 1B).

1.2 | Weight loss: a key cornerstone in NAFLD management

Interventions of diet and exercise as well as other strategies to induce weight loss have been shown to be useful for the treatment of both NASH and fibrosis, as well as to improve many of the comorbidities and risk factors associated with NAFLD. A single-arm trial with 293 patients showed that NASH and fibrosis regress in 90% and 45%, of patients who lost ≥10% weight at 1 year respectively.[21] A recent meta-analysis that included 22 studies (n = 2588) comparing a high percentage of weight loss, no weight loss or less weight loss found that after a median of 6 months of intervention weight loss was significantly associated with improvements in: 1) ALT (standardized mean difference: −9.81 U/L; 95% CI, −13.12 to −6.50); 2) steatosis (−1.48; 95% CI, −2.27 to −0.70); 3) NAS score (−0.92; 95% CI, −1.75 to −0.09); 4) liver stiffness (−1.11 kPa; 95% CI, −1.91 to −0.32), but did not find significant changes in: 1) histologic liver fibrosis (−0.13; 95% CI, −0.54 to 0.27); 2) inflammation (−0.01; 95% CI, −0.10 to 0.07) or ballooning (−0.11; 95% CI, −0.26 to 0.04).[22] This suggests that the percentage of weight loss plays an important role in the potential benefit of these interventions because the average weight loss observed (−3.61 kg; 95% CI, −5.11 to −2.12) was clearly below the 5%-10% decrease in body weight needed to resolve NASH and the regression of fibrosis in the previous study.

Regular physical exercise has several beneficial effects on overall health. While decreasing body mass and adiposity are not the primary outcomes, exercise can mediate several diseases that accompany obesity including T2DM and cardiovascular disease (CVD). Several studies have shown that weight loss can also result in a dose-dependent remission of T2DM. A weight loss of ~15 kg, as part of an intensive management program, can result in remission of T2DM in ~80% of patients with obesity and T2DM. An observational analysis of participants in the Look AHEAD (Action For Health in Diabetes) study (n = 5,145) examined the association between the extent of weight loss and changes in CVD risk factors at 1 year and found that weight changes were significantly correlated with changes in glycaemic control, blood pressure, HDL cholesterol and triglycerides. All of these results suggest that significant weight loss has a clear benefit in patients with NAFLD and most, if not all of the range of comorbidities and risk factors associated with it.[23,24]

Nevertheless, diet- and exercise-based interventions have several important limitations. The difficulty of long-term adherence and the maintenance of initial weight loss are probably one of the major drawbacks of this approach, and strategies to improve it are needed. A meta-analysis including 49 studies identified several energy intake-reducing behaviours and energy expenditure-increasing behaviours associated with long-term adherence and found consistent evidence that demographic factors were not predictive of weight-loss maintenance. On the other hand, behavioural and cognitive factors that promote a reduction in energy intake, an increase in energy expenditure and monitoring this balance were predictive factors. Specifically, self-monitoring factors were found to have a PPV for the maintenance of weight loss. Moreover, several cognitive-psychological factors also indirectly influence the maintenance of weight loss, ie high personal efficacy for exercise and weight management.[25]

Another major limitation is the lack of a general consensus for diet and exercise recommendations and of methods to assess whether patients are actively following intervention programs. Lifestyle protocols are usually at the discretion of the researcher and vary from study to study. There is also a risk of site-specific differences that confound study outcomes even when the same standardized lifestyle recommendations are applied to all participants. The Liver Forum Standard of Care Group recently reviewed this topic evaluating 46 clinical trials available on PubMed and clinicaltrials.gov, and showed that 52% of randomized and investigator-initiated controlled trials did not describe lifestyle modifications at all, 22% had undefined recommendations for diet and/or exercise and 26% had nutritional counselling and/or exercise recommendations. Interpretation of results is challenging without this basic information, especially when early-phase studies also fail to demonstrate a therapeutic response in treatment arms compared to placebo. This group has provided a series of recommendations for early- and late-stage studies that will most likely improve assessment of both diet- and exercise-based interventions.[26]

Surgery can be an option in patients in whom diet and exercise interventions are difficult. Bariatric surgery provides marked long-term weight loss and can prevent the development of the risk factors of CVD such as T2DM, hypertension and dyslipidemia.[27] A recent 5-year longitudinal study in patients who underwent bariatric surgery reported the resolution of NASH in 84% of patients (n = 64; 95% CI, 73.1-92.2) and the regression of fibrosis in 70.2% (95% CI, 56.6-81.6), which completely resolved in 56% (95% CI, 42.4-69.3) including 45.5% of patients with baseline bridging fibrosis.[36] It is interesting to note that in the presence of persistent NASH there was no decrease in fibrosis and less weight loss (reduction in BMI of 6.3 ± 4.1 kg/m^2 in persistent NASH vs 13.4 ± 7.4 kg/m^2 in NASH resolution; P = .017).[28] A recent meta-analysis including 32 cohort studies and 3093 biopsy specimens from bariatric patients showed a biopsy-confirmed resolution of steatosis in 66% of patients (95% CI, 56%–75%), inflammation in 50% (95% CI, 35%–64%), ballooning in 76% (95% CI, 64%–86%) and fibrosis in 40% (95% CI, 29%–51%). This intervention, however, also resulted in new or worsening features

of NAFLD, such as fibrosis, in 12% of patients (95% CI, 5%–20%).[29] Finally, this surgery with its associated risk factors cannot be indicated on a large scale to treat a disease as prevalent as NASH thus, dietary and exercise-based approaches remain the best strategy to manage this disease.

1.3 | Therapeutic landscape for NAFLD

Treatments for NASH and liver fibrosis differ in their mode of action but tend to result in one or more of these outcomes: 1. hepatocyte protection through active elimination of sources that trigger damage; 2. inhibition of signals that drive HSC activation; 3. immune modulation and 4. inhibition of fibrotic scar formation and propagation.

Most treatments in late clinical trials that have included a histological evaluation of tissue have been found to have limited or no efficacy in reversing NASH and fibrosis (Table S1). Emricasan, a pan caspase inhibitor, did not reach the primary objective of improvement in fibrosis without the worsening of NASH (emricasan 5 mg: 11.2%; emricasan 50 mg: 12.3%; placebo: 19.0%; $P = .972$ and .972, respectively) or the secondary objective of resolution of NASH without worsening of fibrosis (emricasan 5 mg: 3.7%; emricasan 50 mg: 6.6%; placebo: 10.5%; $P = .070$ and .335 respectively) [NCT02686762]. Selonsertib, an Ask1 inhibitor, did not improve the regression of fibrosis without worsening NASH in F3 patients (10% 18mg or 12% 6mg vs 13% placebo; $P = .49$ and $P = .93$, respectively) [NCT03053050], or compensated F4 (14% 18 mg or 13% 6 mg vs 13% placebo; $P = .56$ and $P = .93$, respectively) [NCT03053063]. Elafibranor, a PPAR-α and δ dual agonist, has been shown to resolve NASH without worsening fibrosis in a stage 2 trial, but has no effect on liver fibrosis. In addition, a recent press release from the Golden phase III trial reported that Elafibranor did not meet the primary endpoint of histological improvement of NASH (19.2% vs 14.7%; $P = .066$) or fibrosis (24.5% vs 22.4%; $P = .44$) in the interim analysis [NCT02704403]. Similarly, the GLP-1 inhibitor liraglutide has been shown to promote the resolution of NASH in a stage II trial (39% vs 9% placebo) but did not significantly improved fibrosis (26 vs 14%; $P = .46$) [NCT01237119]. The resolution of NASH has also been reported in a preliminary analysis in a stage II trial in which diabetic patients with NASH were treated with semaglutide (59% vs 17% in placebo) [NCT02970942], another GLP1 analogue. Both these agents require further evaluation in larger trials and evaluation for the resolution of fibrosis. Treatment with Aramchol, a liver-targeted SCD1 modulator, resulted in the resolution of NASH (19.2% vs 7.5%; $P = .0462$) as well as resolution of NASH without worsening fibrosis (16.7% vs 5.0%; $P = .0514$) and also a higher, but not significant, proportion of patients with a one-point improvement in fibrosis without the worsening of NASH in Aramchol 600mg vs placebo (29.5% vs 17.5%; $P = .2110$) [NCT02279524]. Cenicriviroc, an antagonist of C-C chemokine ligands 2 and 5 (CCL2 and CCL5) which promote liver fibrosis through activation of inflammatory signalling and immune cell infiltration, resulted in a significant reduction of one stage of fibrosis after 1 year (20% CVC vs 10% placebo; $P = .02$) but this difference was not significant after 2 years of treatment (15% CVC vs 17% placebo) [NCT02217475]. Post-hoc analysis comparing patients with advanced liver disease (F3) showed a greater but non-significant improvement in patients treated with CVC (15.8% vs 4.8% placebo $P = .18$).[30] Finally, Semaglutide has recently proven his ability to revert efficiently NASH (59% vs 17%; $P < .001$) but did not significantly improve fibrosis (43% vs 33%; $P = .48$) [NCT02970942]. The numerous reasons for the high rate of failure in these large trials were recently reviewed.[31,32]

There are currently more than 30 on-going trials (≥ stage2) of new therapies for NAFLD with a histological evaluation of fibrosis (Table S2). Thus far, obeticolic acid, an FXR agonist, is the only compound that has been found to modestly improve fibrosis in a phase III clinical trial interim analysis (resolution of fibrosis by at least 1 stage without worsening of NASH 23% 25 mg dose vs 12% in placebo). This improvement was not accompanied by a resolution of NASH, although several components of the histological NAFLD activity score did improve [NCT01473524]. Pioglitazone is a PPAR-γ analogue that been shown to promote the resolution of NASH in prediabetic and diabetic patients [NCT00994682] but has not been found to significantly improve fibrosis in randomized studies (Table S1). However, a recent meta-analysis including data from 5 trials suggest that this compound could also improve advanced fibrosis (OR, 3.15; 95% CI, 1.25-7.93; $P = .01$) and any stage of fibrosis (OR, 1.66; 95% CI, 1.12-2.47; $P = .01$), even in non-diabetics (OR, 2.95; 95% CI, 1.04-10.90; $P = .02$; for advanced fibrosis and OR, 1.76; 95% CI, 1.02-3.03; $P = .02$ for any stage fibrosis).[33]

1.4 | Concluding remarks

The management of NAFLD requires a multidisciplinary approach to increase detection and referral of patients with advanced fibrosis from primary care centres and non-specialist units, mainly endocrine to hepatology clinics. Patient management should focus on treating comorbidities and risk factors that are more likely to worsen fibrosis and include active and well-designed standardized lifestyle interventions. This disease also requires educational programs to improve awareness of the impact of this silent disease with long-term asymptomatic periods on quality of life and survival. Educational programs, tools and information to central laboratories and outpatient clinics as well as strategies to facilitate easy referral of patients between professionals are needed.

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CONFLICT OF INTEREST

DMM, RGD, JA and PD have no potential conflict of interest. MRG has served as a speaker for AbbVie, Bristol-Myers Squibb, GENFIT, Gilead Sciences, Intercept, MSD and Roche; an advisory

board member for GENFIT, Gilead Sciences, Intercept, Janssen-Cilag, Kaleido, NovoNordisk, Medimmune and Prosceinto; and has received research grants from Abbvie, Gilead Sciences and Intercept.

ORCID

Manuel Romero-Gómez https://orcid.org/0000-0001-8494-8947

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