REVIEW

DOI: http://dx.doi.org/10.15403/jgld-775

Identification of Patients with Advanced Fibrosis Due to Nonalcoholic Fatty Liver Disease: Considerations for Best Practice

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Received: 22.01.2020
Accepted: 02.04.2020

ABSTRACT

Nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) prevalence has increased in the past two decades, resulting in a significant but under-recognised public health burden. This impacts the prevalence of advanced fibrosis, end-stage liver disease and associated extrahepatic manifestations. To understand the challenges in recognising patients with advanced fibrosis due to NASH and develop a standardised approach to screen these patients, the authors of this document provided their opinions and expertise from practice and published evidence to identify key challenges and current approaches for diagnosing NASH. The severity of liver fibrosis due to NASH is the main indicator of associated morbidity and mortality outcomes. Therefore, identifying patients with, or at risk of, advanced fibrosis due to NASH and linking them to appropriate care is critical. This can be challenging due to a lack of awareness of NASH among healthcare professionals and a lack of standardised protocols for identifying patients. Simple noninvasive tests may provide an opportunity to facilitate early identification of these patients. This article proposes a simple, universally applicable diagnostic algorithm for use in clinical practice, that includes sequential use of noninvasive tests, ideally a biological marker and an imaging technique, which may help to facilitate early diagnosis of these patients. In the opinion of the authors, early detection of advanced fibrosis is fundamental in the efforts to halt the progression of NASH and diagnostic algorithms may facilitate pre-emptive interventions to curtail the disease.

Key words: advanced fibrosis – best practice – identification – NAFLD – NASH.

Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; APRI: the AST-to-platelet ratio index; ARFI: acoustic radiation force impulse; DeMILI®: Detection of Metabolic-Induced Liver Injury; ELF: Enhanced Liver Fibrosis test; FIB-4: fibrosis-4 score; HCC: hepatocellular carcinoma; HCP: healthcare professional; NAFLD: nonalcoholic fatty liver disease; NASH: nonalcoholic steatohepatitis; NFS: NAFLD fibrosis score; NIT: noninvasive test; SWE: shear wave elastography; T2DM: type 2 diabetes mellitus.

EPIDEMIOLOGY AND DISEASE BURDEN

Chronic liver disease is a significant public health issue, affecting approximately 844 million people worldwide and accounting for 2 million deaths annually [1]. In recent years, nonalcoholic fatty liver disease (NAFLD) has surpassed viral hepatitis as the most common aetiology of chronic liver disease [1–3].

Approximately 25% of the global population have NAFLD [4], of whom 25% will develop nonalcoholic steatohepatitis (NASH), the progressive form of the disease [5]. A modelling study suggests that by 2030, the prevalence of NASH will rise by up to 56%, with liver mortality and advanced liver disease expected to more than double [6].

The rapid increase in NAFLD/NASH has already impacted on the incidence of late-stage liver disease. In the USA, the rate of NAFLD-associated advanced fibrosis and NASH cirrhosis has increased by more than 2-fold over the past two decades [7]; in many European countries, NASH mortality is projected to double in the next two decades [6]. NASH is currently the second leading indication for liver transplantation and liver transplantation waitlist registration in the USA [8], and the most rapidly growing cause of hepatocellular carcinoma (HCC) among USA patients listed for liver transplantation [9]. In the UK, NAFLD patients present with larger tumours that are less likely to be amenable to curative therapy compared with patients with viral hepatitis C [10]. Therefore, there is an urgent need to address the already significant impact of NASH, particularly as the annual direct NAFLD-associated medical costs are estimated to be around $103 billion in the USA, and €35 billion in Europe [11].

The presence and severity of NASH is associated with type 2 diabetes mellitus (T2DM), as well as a greater prevalence and incidence of cardiovascular disease and chronic kidney disease; it may also be a risk factor for colorectal neoplasia [12, 13]. Patients with T2DM are particularly susceptible to more severe forms of NAFLD and its associated consequences [14, 15] as they have a higher prevalence of advanced fibrosis compared with the general population [16]; approximately 10% of people with T2DM have advanced liver disease [15]. These associations imply that identifying patients with NASH would allow for increased surveillance and potentially earlier intervention to reduce the risk of hepatic, cardiovascular and renal complications.

THE IMPORTANCE OF IDENTIFYING PATIENTS WITH ADVANCED FIBROSIS DUE TO NAFLD/NASH

In patients with NASH, analyses of sequential liver-biopsy specimens indicate that fibrosis progresses at a rate of approximately one stage every 7 years, suggesting that moderate fibrosis (fibrosis stage [F]2) progresses to cirrhosis (F4) within 20 years [5]. However, a number of studies have indicated that the rate of progression varies widely [17–19]. Detecting fibrosis in patients with NASH is critical as the degree of fibrosis independently predicts the development of liver-related complications, the need for liver transplantation, and liver-related and overall mortality in patients with NAFLD [20–22]. Degree of fibrosis is also associated with a higher incidence of chronic kidney disease and increased cardiovascular disease-related mortality [23]. Nevertheless, despite its high prevalence and the potential consequences of inaction, studies suggest that NAFLD/NASH is largely under-recognised [24–26]. Therefore, there is a pressing need to identify patients with advanced fibrosis and cirrhosis, so that they can be managed to delay further progression, especially given the large number of patients with undiagnosed cirrhosis within the general population (6–7%) [27].

Key summary points:
- There is an urgent need to address and manage NASH as the associated clinical and economic burden is predicted to double in the next decade.
- In the authors' opinion, healthcare professionals (HCPs) should be more proactive in identifying patients with advanced fibrosis due to NASH, as fibrosis stage is a predictor for hepatic and extrahepatic morbidity and mortality.
- This is particularly important due to the significant prevalence of silent cirrhosis in the general population, specifically in patients with T2DM.

THE CHALLENGE OF IDENTIFYING PATIENTS WITH ADVANCED FIBROSIS DUE TO NAFLD/NASH

Identifying individuals with advanced fibrosis due to NAFLD/NASH allows for management strategies to be put in place, which may improve patient outcomes and potentially reduce future healthcare burdens. However, there is a general lack of awareness of NAFLD/NASH among HCPs, particularly in primary care and non-liver specialists such as endocrinologists [28–30]. The accompanying lack of awareness of treatments in clinical development for NASH [28] may also lead to a lack of motivation to identify at-risk patients, and a belief that the associated comorbidities of NASH are the responsibilities of other specialists.

Lack of awareness among HCPs is compounded by a lack of standardisation within the guidelines. Whilst some national and international guidelines support screening of high-risk populations for NAFLD/NASH, there is a lack of consensus regarding the value of screening individuals. Guidelines predominantly cite uncertainties around diagnostic tests and treatment options, and a lack of real-world evidence supporting long-term benefits and cost-effectiveness of screening [31, 32]. While the authors do not advocate large national-scale efforts until cost-effectiveness data has been published, targeted initiatives to identify and refer patients with advanced fibrosis can address an unmet need.

The utility of liver biopsy, considered to be the 'gold standard' for diagnosing fibrosis in patients with NAFLD/NASH, is limited by cost, accuracy, risk of adverse events and invasiveness, making it unsuitable for large-scale screening [33–35]. Therefore, simple, easily accessible, validated noninvasive tests (NITs) are critical. This document will distil the performance reviews of these NITs into a simple, practical, universally applicable algorithm for use in a variety of clinical settings, to reduce the challenges associated with identifying high-risk patients with NASH.

Key summary points:
- Consensus is lacking regarding the value of screening individuals for NAFLD/NASH due to uncertainties around diagnostic tests and treatment options, and a lack of evidence supporting the long-term benefits and cost-effectiveness of screening.
- Due to the development of reliable NITs to identify patients with advanced fibrosis, there is now potential to put management strategies in place earlier.

CONSIDERATIONS FOR IDENTIFYING PATIENTS WITH ADVANCED FIBROSIS DUE TO NAFLD/NASH

Prior to designing a strategy to identify and manage patients with advanced fibrosis due to NASH, population demographics, healthcare systems and availability of techniques need to be considered.

Which patient populations should be screened?

NAFLD/NASH induce non-specific and generally prevalent symptoms [36, 37]; a large proportion of cases may be asymptomatic until patients develop decompensated cirrhosis [38–40]. Screening is therefore essential to ensure that patients, particularly those with advanced fibrosis (F3–F4), are identified and linked to care.

Current guidelines do not recommend widespread or community screening, mainly due to the perceived associated direct and indirect medical costs [31, 32, 41]. However, some national and international initiatives (ETHON project, Spain [42]; international LiverScreen project [NCT03789825]) are currently investigating the effectiveness of screening the general population for significant liver disease, considering evidence that this may be a cost-effective strategy.

Table I. Guideline recommendations: screening for NAFLD fibrosis

Guidelines	Recommendations	Recommended noninvasive tests
AASLD [32]	• Routine screening for NAFLD in high-risk groups attending primary care, diabetes or obesity clinics is not advised at this time because of uncertainties surrounding diagnostic tests and treatment options, along with lack of knowledge related to long-term benefits and cost-effectiveness of screening	• NFS or FIB-4 index for identifying NAFLD patients with higher likelihood of bridging fibrosis (F3) or cirrhosis (F4) • VCTE or MRE for identifying advanced fibrosis in patients with NAFLD
EASL [31]	• Patients with insulin resistance and/or metabolic risk factors (i.e. obesity or MetS) should undergo diagnostic procedures for the diagnosis of NAFLD • All individuals with steatosis should be screened for features of MetS, independent of liver enzymes. All individuals with persistently abnormal liver enzymes should be screened for NAFLD • In subjects with obesity or metabolic syndrome, screening for NAFLD by liver enzymes and/or ultrasound should be part of a routine work-up. In high-risk individuals (age > 50 years, T2DM, MetS) case finding of advanced disease (i.e. NASH with fibrosis) is advisable	• NFS, FIB-4, ELF, FibroTest for diagnosis of at-risk patients with US-confirmed steatosis and normal liver enzymes and monitoring of low-risk patients with steatosis
Asia-Pacific Working Party [107]	• Screening of NAFLD may be considered in at-risk groups such as patients with T2DM and obesity	• NFS, FIB-4, BARD score, ELF, FibroTest, FibroMeter, HepaScore have shown reasonable diagnostic accuracy. Concerns regarding definition of threshold values in Asian patients: "at the present time, the clinical use of such tools to avoid liver biopsy remains undefined"
NICE [108]	• Offer testing for advanced liver fibrosis to people with NAFLD	• ELF
WGO [41]	• The diagnosis should be sought in all patients who present with risk factors for NASH	• None; insufficient data; costs; limited availability Recommends liver biopsy
Japanese Society of Gastroenterology and Japanese Society of Hepatology [109]	• Not specified	• No practically useful surrogate markers for diagnosing NASH NFS for predicting severity of fibrosis
Belgian Association for the Study of the Liver [110]	• The following populations are at high risk for NAFLD and should be screened by their general practitioner or the specialists involved: presence of the metabolic syndrome or its components, patients with obesity (BMI ≥ 30 kg/m2), patients with T2DM or patients with a history of ischemic CVD	• FIB-4 and NFS with age-appropriate cut-offs and US-based elastography are acceptable for identifying patients at low risk of advanced fibrosis/cirrhosis • Combine for increased accuracy Other tests (e.g. ELF, FibroTest) can be used according to local expertise, but are proprietary and not reimbursed
Italian Association for the Study of the Liver [111]	• As per EASL guidelines	• For the diagnosis of NASH biochemical tests or imaging techniques cannot distinguish NASH from simple steatosis and liver biopsy remains the reference standard

AASLD: American Association for the Study of Liver Diseases; BARD: body mass index, AST/ALT ratio, and diabetes; BMI: body mass index; CVD: cardiovascular disease; EASL: European Association for the Study of the Liver; ELF: Enhanced Liver Fibrosis test; FIB-4: Fibrosis-4 score; MetS: metabolic syndrome; MRE: magnetic resonance elastography; NAFLD: nonalcoholic fatty liver disease; NASH: nonalcoholic steatohepatitis; NFS: nonalcoholic fatty liver disease score; NICE: National Institute for Health and Care Excellence; T2DM: type 2 diabetes; US: ultrasound; VCTE: vibration-controlled transient elastography; WGO: World Gastroenterology Organisation

Screening at-risk patients has been shown to be cost-effective in several studies across different countries [43–45]. With the exception of the current American Association for the Study of Liver Diseases (AASLD) guidelines, most national and international guidelines recommend screening in 'high-risk' populations (Table I). AASLD guidelines recognise obesity and T2DM as two of the most common comorbidities among NASH patients [32], providing motivation towards specifically screening these populations. Until there is more alignment between different guidelines or robust evidence of the benefits of screening the general population, the authors believe that screening at-risk populations is an appropriate starting point for identifying more patients with advanced fibrosis due to NASH.

Key summary points:

- Screening patients as per current guideline recommendations aims to ensure that those in greatest need will be effectively identified and managed.
- Identifying these patients early through effective screening will link them to care before they develop late-stage liver disease.
- Initiatives are underway to investigate the effectiveness of screening in both the general and at-risk populations.
- The authors believe that avoiding the development of late-stage liver disease, particularly in at-risk patients, will be more cost-effective in the long term.

Which screening tests to use?

Given the limitations of biopsy for widescale screening, the authors believe that NITs should play an increasing role in detecting NASH. The efficacy and accuracy of these techniques have been described previously in several review articles [46–49], so will only be covered briefly here.

Two main types of NIT are used; predictive models and serum biomarkers which use clinical and laboratory data (Table II), and imaging techniques (Table III) which estimate liver stiffness as a potential surrogate of hepatic fibrosis.

Table II. Combination scores of noninvasive serum biomarkers of liver fibrosis in NAFLD (adapted from Chin et al, 2016) [54]

Index	Parameters	Number of NAFLD patients	AUROC for advanced fibrosis	Sensitivity	Specificity	NPV	PPV
AST/ALT ratio [112]	AST, ALT	145	0.83	74	78	93	44
BARD [113–115]	BMI, AST, ALT, DM	827	0.81	-	-	-	-
		145	0.77	89	44	95	27
		138	0.67	51	77	81	45
		1038	0.76	74	66	-	-
FIB-4 [112,115,116]	Platelet count, AST, ALT, age	145	0.86	85	65	95	36
		541	0.80	52	90	-	-
		1038	0.85	84	69	-	-
FibroMeter [117]	Platelet count, prothrombin index, AST, a2-macro-globulin, hyaluronic acid, urea, age	383	0.89†	81†	84†	77†	86†
FibroTest [118]	Haptoglobin, α2-macro-globulin, apolipoprotein A1, GGT, bilirubin, age, gender	267	0.81	92	71	98	33
NFS [53,112,115]	Age, BMI, platelets, AST/ ALT, albumin, IFG/diabetes	733	0.82–0.88	77–82	71–77	88–93	52–56
		145	0.81	33–78	58–98	86–92	30–79
		1038	0.84	77	70	-	-
ELF score [59,119]	Hyaluronic acid, TIMP-1, age, MMP-3	61	0.87	89	96	96	80
		192	0.90	80	90	94	71
APRI score [112]	AST, platelet count	145	0.67	27	89	84	37

†Values are for prediction of significant fibrosis. ALT: alanine amino transferase; APRI: AST-to-platelet ratio index; AST: aspartate aminotransferase; AUROC: area under the receiver operating characteristics curve; BMI: body mass index; DM: diabetes mellitus; ELF: Enhanced Liver Fibrosis blood test; FIB-4: Fibrosis-4 score; GGT: γ-glutamytransferase; IFG: impaired fasting glycemia; MMP: matrix metalloproteinases; NAFLD: nonalcoholic fatty liver disease; NFS: nonalcoholic fatty liver disease fibrosis score; NPV: negative predictive value; PPV: positive predictive value; TIMP: tissue inhibitors of metalloproteinases

Serum biomarkers are readily available and may be able to exclude a large proportion of the population at low risk [50]. Of the simpler models, aspartate aminotransferase/alanine aminotransferase (AST/ALT) ratio, the NAFLD fibrosis score (NFS), Fibrosis-4 (FIB-4) score, the AST-to-platelet ratio index (APRI), and the BARD score (BMI, AST/ALT ratio and T2DM) are the most widely used and have been validated worldwide (Table II) [51–55].

FIB-4 and NFS are particularly promising tools based on readily available variables (Table II), and can be easily calculated using freely available online calculators [53]. Both tools have good negative predictive values and negative likelihood ratios and can reliably and relatively inexpensively exclude advanced fibrosis, thus identifying lower risk patients who do not need secondary care referral. However, although FIB-4 and NFS are effective at excluding advanced fibrosis, as well as predictive of liver outcomes over time [56], they have limited ability in differentiating between earlier stages of fibrosis [57]. The relative risk at earlier stages is unclear [58].

Commercial biomarker panels such as the Enhanced Liver Fibrosis (ELF™) test, FibroTest® (FibroSure®) and FibroMeter® are also available, though they are more expensive and less widely available than FIB-4 and NFS. ELFTM is a simplified algorithm comprising a number of parameters (Table II), which can distinguish advanced fibrosis (≥F3) with an area under the receiver operating characteristics curve (AUROC) of 0.90 [59]. It may also be a good predictor of liver-related morbidity and mortality [60]. Therefore, in specialist secondary clinics, this technique may be useful in identifying the presence of advanced fibrosis, though the cut-offs need to be adjusted according to age and sex [61].

Several new scoring systems have also reported good accuracy in detecting advanced fibrosis in patients with NASH. These include the FM-fibro index [62, 63] an algorithm based on the measurement of serum PRO-C3 (a marker of type III collagen formation), age, presence of diabetes and platelet count (ADAPT) [64]. There is also the NIS4 scoring system [65] and the CA index, which is based on the combination of type IV collagen 7S and AST, and is inexpensive and simple to use [66]. Wisteria floribunda agglutinin-positive (WFA+)-Mac-2-binding protein (Mac2BP) levels and type 4 collagen 7S levels, alone and in combination, have been shown to be useful independent markers for detecting fibrosis in NAFLD [67]. In addition, the Hepamet Fibrosis Score has recently demonstrated superior diagnostic accuracy, compared with FIB-4 and NFS, in a multinational cohort of 1500 patients [68–70].

Biomarkers and scoring systems are not available universally and this is an important consideration before implementation. Differences in ethnicity can also impact NITs, as FIB-4 and NFS have been shown to perform less well in South Asians compared with Caucasians [71].

In addition to the biomarkers and scoring systems, there are imaging techniques such as magnetic resonance elastography and transient elastography (FibroScan®) (Table III) [72–74]. FibroScan® has good diagnostic accuracy for the presence of fibrosis (≥F1) and advanced fibrosis (≥F3), with AUROC of 0.93 for both [75–77]. Its high negative predictive value makes

Table III. Features of imaging biomarkers (adapted from Wong et al, 2018 [78])

Test	Description	AUROC	Reproducibility	Feasibility	Limitations
USG	The echogenicity, or brightness, of tissue depends on the degree of beam scattering by the tissue (fat deposition in tissue accentuates scattering) advanced fibrosis	0.93 for diagnosis of steatosis (Sn 60–80%, Sp 80–100%)	Reliability: kappa statistics ranging from 0.54 to 0.92 for intrarater reliability and from 0.44 to 1.00 for interrater reliability	• Easy to perform and interpret • No radiation • Available in extremely high numbers across medical centres across the world • Low cost	• Low sensitivity for mild steatosis • Operator-dependent • Reduction of Sn and Sp in patients who are obese and those with advanced fibrosis
Controlled attenuation parameter	Measurement of the degree of ultrasound attenuation by hepatic fat using a process based on simultaneous TE	0.82 for diagnosing any steatosis (Sn 69%, Sp 82%) 0.86 for diagnosing stage 2 and stage 3 steatosis (Sn 77%, Sp 81%) 0.88 for diagnosing stage 3 steatosis (Sn 88%, Sp 78%)	Concordance correlation coefficient 0.82	• Immediate assessment of steatosis • Ambulatory clinic setting • Simultaneous liver stiffness measurement • Failure rate < 10%	• Does not reliably differentiate between steatosis grades
MRI-PDFF	PDFF measurement is an option that can be added to MRI scanners to quantitatively assess steatosis	AUROC 0.99 for diagnosing any steatosis (Sn 96%, Sp 100%, PPV 1.00, NPV 0.70)	ICC > 0.90	• Not affected by obesity • Simultaneous MRI for liver architecture and carcinoma and MRS for steatosis	• Costly • Time consuming • Requires MRI facility • Might be inaccurate in acute inflammation or iron overload • Cannot be used in some patients with implantable devices
MRS†	• Assesses liver triglyceride content • Provides a collection of spectra for signal fat fraction estimation, which requires a proper acquisition technique in order to estimate the fat	• Sn 89% and Sp 92% for diagnosis of liver fat with a threshold of 0–5% fat • Sn 83% and Sp 94% for diagnosis of 10% liver fat • Sn 73% and Sp 96% for diagnosis of liver fat > 30%	Very high with ICC 99.8%	• The absolute liver fat concentration can be directly measured, and very small amounts of liver fat (as low as 0.5%) can be detected and quantified	• Complex and time-consuming data analysis • Data collection occurs from a small portion of the liver (within a voxel ≤ 3 cm × 3 cm × 3 cm), which might be subject to sampling error

†AUROC not available. AUROC: area under the receiver operating characteristics curve; ICC: intraclass correlation coefficient; MRI: magnetic resonance imaging; MRS: magnetic resonance spectroscopy; NPV: negative predictive value; PDFF: proton density fat fraction; PPV: positive predictive value; Sn: sensitivity; Sp: specificity; TE: transient elastography; USG: ultrasonography

it a useful screening tool to rule out the presence of fibrosis and differentiate between early and advanced fibrosis [57], but its positive predictive value for ruling in advanced fibrosis or cirrhosis is modest [78].

Other imaging techniques include acoustic radiation force impulse (ARFI), which combines elastography and conventional B-mode ultrasonography to measure liver stiffness [79]. Techniques that use shear wave elastography (SWE) technique have demonstrated significant correlation with histologic scores [80] and can assess liver stiffness by measuring the velocity of elastic shear waves in the liver parenchyma [81]. Two-dimensional SWE shows promise in the non-invasive staging of liver fibrosis in patients with NAFLD, although cut-offs need to be optimised [82]. Additionally, there is the LiverMultiScanTM which uses multiparametric MRI to provide quantitative measures of liver fat, iron, fibrosis and inflammation [83] and the DeMILI® (Detection of Metabolic-Induced Liver Injury) software, which can detect NASH and predict significant fibrosis [84]. Both the LiverMultiScanTM and DeMILI have been utilised in the Liver Investigation: Testing Marker Utility in Steatohepatitis (LITMUS) project, which aims to develop and validate qualification biomarkers that diagnose and/or monitor NAFLD/NASH progression and fibrosis stage [85].

Despite the advances in imaging techniques, these technologies are not routinely available in primary care and are more often used once a suspicion of NASH-related fibrosis has been identified through predictive models and serum biomarkers. Therefore, their use in large-scale screening may be limited, and may be more applicable in specialist secondary care clinical settings.

Some studies have also reported that certain tests may be less sensitive or require modification in some populations, such as morbidly obese patients [86, 87]. Obesity is associated with limited liver ultrasound sensitivity when diagnosing and monitoring changes in hepatic steatosis over time [88]. Using a semiquantitative ultrasonographic scoring system can improve the performance but can be time-consuming [88]. The FibroScan® XL probe should be used where possible as it has a more sensitive ultrasound transducer and a greater depth of measurement, making it more appropriate for overweight and obese patients [89–91]. The M probe still provides useful information when it is the only option available [91], though its limitations need to be considered for the 5% of patients

who fail transient elastography measurements and the 15% of patients with unreliable results due to obesity [91–94].

Overall, recommendations regarding the most appropriate techniques cannot be made due to their differing availabilities in different countries and clinical settings. However, in the opinion of the authors, the increasing number of well-validated NITs does allow for a small selection to be suggested (with alternatives) which can be applied to most clinical centres.

Key summary points:

- Currently available NITs, such as predictive models, serum biomarkers and imaging techniques, can be viable alternatives to the invasive liver biopsy.
- Simple, easy-to-use NITs may be more appropriate for large-scale screening and are therefore particularly useful to include in a referral pathway or model of care.
- The authors suggest that NITs can be used as part of a simple strategy to exclude low-risk patients and identify patients at risk of advanced fibrosis due to NASH.

WHAT COULD A SIMPLE PATHWAY FOR IDENTIFYING PATIENTS LOOK LIKE?

After careful review of the tools available, the authors believe there is an opportunity to develop a simple, widely applicable pathway for identification of patients with NASH, that enables an accepted theory to be put into practice. This pathway should include specific details of the target population and the sequential use of two NITs. For example, the first NIT (usually in primary care or diabetology) should exclude low-risk patients using a readily available, high specificity/negative predictive value NIT (such as FIB-4 or NFS). The second step (in a specialist care setting) should identify high-risk patients for management in liver clinics and return false-positive patients to primary care for regular follow-up.

Several sequential pathways and algorithms to identify or screen for patients with advanced fibrosis due to NASH have already been developed and utilised in clinical practice. However, these pathways have been tailored to be applicable for a national or regional healthcare system. Therefore, we propose the development of a simple pathway which would be adapted to various geographical locations and clinical settings. Although the lack of a prescriptive algorithm could be considered a limitation, we believe the provision of a simple framework for local adaptation is the key to the earlier diagnosis of patients with advanced fibrosis due to NASH.

Fig. 1 shows a simple pathway developed by the authors of this document. The pathway targets screening of patients with features of metabolic syndrome who are at risk of advanced fibrosis due to NASH. This is in line with guideline recommendations to screen this high-risk group [31], which is relatively easy to identify in routine care [32, 95].

When a single NIT is used to identify patients, a significant number may have a score between the established cut-offs, suggesting inconclusive results or an indeterminate stage of fibrosis [96]. The sequential use of NITs can reduce rates of secondary and tertiary referrals and achieve greater cost savings compared with single NITs [97, 98]. In one study, sequential

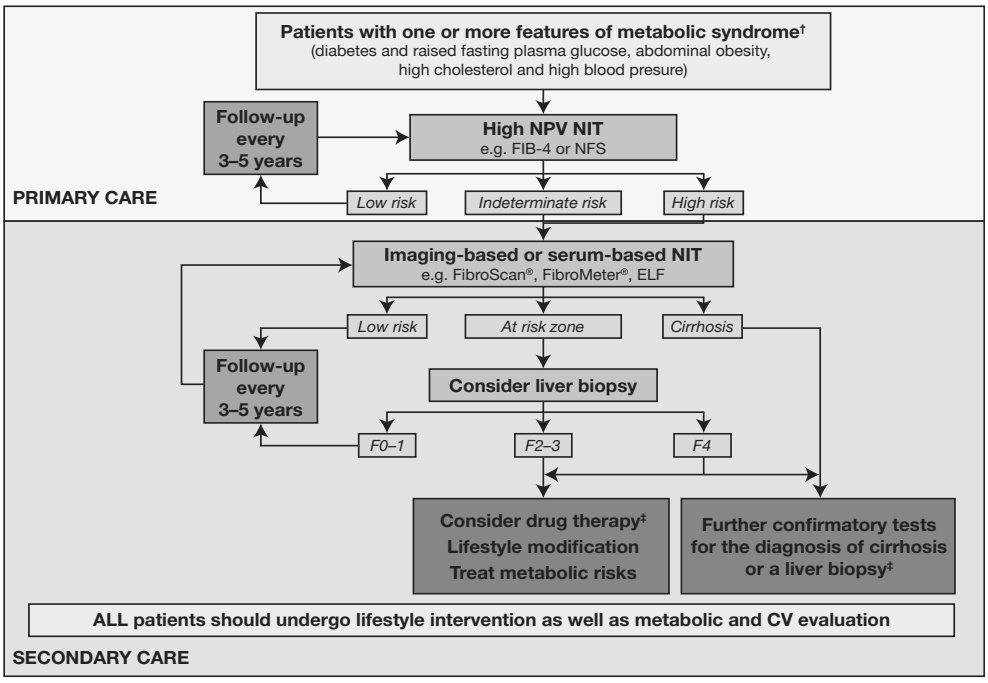

Fig. 1. Proposed testing and referral pathway for the identification and management of patients with advanced fibrosis due to NASH. Due to differences in availability, specific noninvasive tests have only been suggested as examples.
†For further details on metabolic syndrome please refer to the International Diabetes Federation (IDF) consensus worldwide definition of the metabolic syndrome [120]. ‡Consider a clinical trial if available. Patients with F4/cirrhosis and hepatic decompensation (Child class B or C) and/or development of HCC who are not candidates for a clinical trial should be referred for liver transplant evaluation. CV: cardiovascular; ELF: enhanced liver fibrosis; F: fibrosis stage; FIB-4: fibrosis-4; HCC: hepatocellular carcinoma; NFS: NAFLD fibrosis score; NIT: noninvasive test; NPV: negative predictive value.

two-step testing with FIB-4 and ELFTM reduced unnecessary referrals by 80% and resulted in a 3-fold improvement in the detection of cirrhosis [99]. Therefore, the authors recommend adopting an algorithm using sequential testing, where intermediate results indicate a second NIT.

The pathway proposed in Fig. 1 includes sequential use of either FIB-4 or NFS, which do not require specialised equipment, can be calculated using online tools and is favoured by treatment guidelines and other published algorithms [31, 32, 99–103]. The choice between FIB-4 or NFS can be based on local availability and physician preference. Some data suggest that FIB-4 performs better than NFS in obese patients [100].

If patients present with results indicative of an intermediate or a high risk of advanced fibrosis (i.e. if advanced fibrosis cannot be excluded) following the initial round of scoring/biomarker testing, they should be referred to secondary/specialist care. Examples of secondary tests suggested in the proposed pathway that can be carried out in specialist clinics include ELFTM and FibroScan®, which are commonly cited secondary tests in other pathways and algorithms [100–104]. FibroScan® in particular is recommended by the AASLD to identify patients with advanced fibrosis [32]. Unlike NFS and FIB-4, FibroScan® measures fibrosis directly and is more applicable to a specialist clinic.

Patients in whom advanced fibrosis cannot be excluded following the secondary test should be considered for liver biopsy, ensuring that only the most uncertain cases are referred for this expensive and invasive procedure. Patients at high risk of NASH cirrhosis should also be considered for HCC surveillance (using ultrasound) and variceal screening (using FibroScan®) with the Baveno VI criteria [104–106]. Following secondary testing, patients with significant or advanced fibrosis should be monitored every 1–2 years, or every 3–5 years for those at low risk of advanced fibrosis.

The proposed pathway focuses on hepatology. We acknowledge that for it to be effective, engagement with HCPs from different medical disciplines is critical. How to achieve this is not always clear and will vary between countries. In addition, knowledge around the natural history of NASH continues to expand and the cost-effectiveness of screening will change when effective treatments for NASH become available; researchers should provide updated information to guide practice.

Key summary points:

- A simple pathway has been developed to encourage HCPs to screen and identify patients with advanced fibrosis due to NASH (Figure 1).
- Use of a pathway that includes sequential use of NITs, ideally with the use of a biological marker and an imaging technique, is recommended.
- The pathway should be tried in different settings and modified according to local needs.
- The pathway should be refined regularly based on the latest knowledge to provide up-to-date guidance for practice.

CONCLUSIONS

NASH-related fibrosis represents a major and increasing public health issue which is largely under-recognised. Fast, simple and accessible NITs such as FIB-4, NFS, FibroScan® and ELF may provide an opportunity to ensure early identification of patients with advanced fibrosis due to NASH. We believe that the adoption of a simple pathway as described in this manuscript should help to educate HCPs (both in primary and secondary care) on the importance of screening for advanced fibrosis due to NASH. This will be essential if the associated burden is to be ameliorated.

Conflicts of interest: S.A. has served as a speaker for Gilead Sciences, Menarini, MSD and Novartis; a consultant for Ferrer, Gilead Sciences, Intercept, IQVIA, Novartis and Pfizer; an advisory board member for Gilead Sciences, Intercept, IQVIA, Novartis and Pfizer; and has received research funding from Gilead Sciences. A.A. has served as a consultant and advisory board member for Gilead Sciences and Intercept and has received research funding from Gilead Sciences and Intercept. N.A. has served as a speaker for AbbVie, Alexion, Allergan, Eisai, Exelixis Intercept and Salix; a consultant for Allergan, Gilead Sciences and Intercept; and has received research funding from Ackero, Albireo, Allergan, Boehringer Ingelheim, Bristol-Myers Squibb, Galmed, Genfit, Gilead Sciences, Intercept, Madrigal, MedImmune, Novartis, Novo Nordisk, Pfizer, Poxel and Zydus. A.C. has served as a speaker for Gilead Sciences, Shire, Falk-Foundation, AbbVie, Novartis and Alexion. L.C. has served as a speaker for Janssen; an advisory board member for Gilead Sciences, Intercept and Norgine; and has received research funding from AbbVie. A.N. has served as a consultant for EA Pharma Co. Ltd. T.O. has served as an advisory board member for Gilead Sciences Ltd. S.P. has served as a speaker and/or advisory board member for AbbVie, Gilead Sciences and Intercept. V.R. has served as a consultant for Allergan, Boehringer, Bristol Myers Squibb, Galmed, GENFIT, Intercept and Pfizer. E.A.T. has served as a speaker for Gilead Sciences and Intercept and an advisory board member for Gilead Sciences, Intercept, Pfizer and Promethera. V.W.S.W. has served as a speaker for Bristol-Myers Squibb, Echosens, Gilead Sciences and Merck; a consultant and/or advisory board member for 3V-BIO, AbbVie, Allergan, Boehringer Ingelheim, Center for Outcomes Research in Liver Diseases, Echosens, Gilead Sciences, Intercept, Janssen, Novartis, Novo Nordisk, Perspectum Diagnostics, Pfizer, TARGET-NASH and Terns; and has received research funding and served as an advisor for Gilead Sciences. M.R.G 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; has received research grants from Abbvie, Gilead Sciences and Intercept; and co-owns DeMILI (noninvasive magnetic resonance-based method for diagnosing nonalcoholic steatohepatitis).

Authors' contribution: All authors made substantial contributions to the conception of this work and all were involved in critically reviewing and revising each draft for important intellectual content. All authors have approved the final submitted version and agree to be accountable for all aspects of the work. Guarantor of article: Professor Manuel Romero-Gómez takes responsibility for the integrity of the work as a whole, from inception to published article.

Acknowledgements: Medical writing support was provided by Helen Davies and Selene Jarrett of Elements Communications Ltd and funded by Gilead Sciences Europe Ltd.

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