NAFLD: Diagnostic Algorithms for Regulating Patient Fluxes

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ABSTRACT:

Background: The global prevalence of NAFLD is estimated to be over 25% and it is already the leading cause of chronic liver disease in industrialized countries, as a consequence of the spread of obesity and metabolic syndrome. The prognosis of NAFLD is generally benign in the absence of fibrosis, but liver fibrosis rapidly progresses in 20% of the cases and can lead to cirrhosis and/or HCC. **Objective**: This review analysis focuses on non-invasive fibrosis testing strategies for patients with NAFLD in order to increase the efficiency and effectiveness of diagnosis and care, regulating secondary care referral fluxes.

Conclusion: An integrated management plan between primary care and secondary care with a defined algorithm of non-invasive testing to stratify the risk of NAFLD fibrosis is indispensable to increase the early diagnosis of fibrosis but also decrease unnecessary referrals.

KEYWORDS:

Steatohepatitis, non-invasive fibrosis tests, primary care, FIB-4, FIbroscan, ELF, cirrhosis.

1. INTRODUCTION

Non-alcoholic liver disease (NAFLD) is characterized by evidence of excessive storage of fat in hepatocytes, detected by imaging techniques or histology, after the exclusion of other secondary causes of fat accumulation.[1]

The global prevalence of NAFLD is estimated to be over 25% and it is rapidly becoming the leading cause of chronic liver disease in industrialized countries. The reason for this is associated with the widespread increase in the prevalence of the metabolic syndrome (MetS) components, namely obesity, type II diabetes, hypertension, and dyslipidemia. [2]

The term NAFLD encompasses a spectrum of liver manifestations ranging from simple steatosis, with absent or minimal lobular inflammation, to non-alcoholic steatohepatitis (NASH) characterized by hepatocyte ballooning degeneration and lobular inflammation, that could lead to fibrosis and potentially cirrhosis and hepatocellular carcinoma (HCC).

The etiopathogenesis behind this evolution is unknown, likely because of a complex interplay of environmental and genetic factors; however, certain health conditions, such as obesity, hypertension, and diabetes, increase the risk of developing NASH and fibrosis [3].

The prognosis of NAFLD is generally benign in the absence of fibrosis, but liver fibrosis rapidly progresses in 20-30% of the cases and can lead to cirrhosis and/or HCC [4] NAFLD confers increased cardiovascular disease (CVD) risk; in particular, NASH is associated with an increased standardized mortality ratio compared with the general population, while liver disease is only the third most common cause of death after CVD and cancer.[1]

Identifying patients with NAFLD and NASH is nowadays a challenge, as screening in the general population is not advocated or recommended by learned societies. Most diagnoses are generally done incidentally due to a slight increase of aminotransferase levels or an incidental finding of fatty liver in a radiographic study performed for other reasons. Therefore, most patients with NASH remain unrecognized and progress silently until cirrhosis and complications. On the other hand, since the vast majority of patients with NAFLD do not progress to fibrosis, guidance for primary care physicians and non-hepatology specialties is essential for assessing and selecting those patients with NAFLD and fibrosis in order to rationalize referrals.

As NAFLD is a disease of high prevalence and relatively low severity, the primary care physicians' role is crucial. They should be actively involved in the screening and management of patients with community-based pathways to stratify the risk of liver disease and triage secondary care referrals [5]. Moreover, primary care physicians should take care of the follow-up and treatment of patients deemed at low risk.

In this review, we discuss potential strategies and screening algorithms for patients with NAFLD in order to regulate fluxes but also increase the efficiency and effectiveness of their management.

2. EPIDEMIOLOGY

The prevalence of NAFLD is elevated in all continents: the highest rates are reported in the Middle East (32%) and South America (31%), followed by Asia (27%), the USA (24%) and Europe (23%), whereas NAFLD is less common in Africa (14%).[2] Worryingly, it is also present in 7% of normal-weight people.[6] Between 2005 and 2010, the prevalence of NAFLD had increased from 15% to 25% and similarly the rate of NASH in the same timeframe has almost doubled from 33% to 59% [2].

Furthermore, people who have NAFLD in the United States will increase by 21% from 83.1 million cases in 2015 to 100.9 million cases in 2030 in a forecast model elaborated by Estes et al; similarly, the prevalence of NASH will increase by 63% from 16.5 million to 27 million cases.[7]

A small number of studies had analyzed the incidence of NAFLD in the general population, which is reported to be 20-86/1000 person-years based on ultrasonography and/or elevated liver enzymes[8]–[11]. Moreover, the incidence of NAFLD was estimated to be 34 per 1,000 person-years in a population without fatty liver studied at the baseline and after an interval of 3 to 5 years with the combination of H-MRS and transient elastography. [12]

The above suggests that robust systems to identify people at risk of liver disease progression are required as every single patient cannot be assessed by a liver specialist.

3. RISK FACTORS ASSOCIATED WITH NAFLD

Both modifiable and non-modifiable host and environmental factors have been associated with the prevalence and progression of NAFLD.

A strong association between the MetS and/or its components [13] and NAFLD has been established. In particular, the study of Smits et al illustrated that the prevalence of NAFLD is proportionally related with the number of MetS criteria, from a percentage as low as 17.2% in the group of subjects who meet none of the MetS criteria, reaching 90.8% in those who meet all five.[14]

There is also a linear relationship between the prevalence of NAFLD and BMI: in non-obese subjects (BMI<25 kg/m^2) the prevalence is under 20%, in those with a BMI ranging from more than 25 kg/m^2 to less than 30 kg/m^2 it is approximately 50%, and in those with a BMI over 30 kg/m^2 it reaches 80%. [15][16].

NAFLD is prevalent in over 60% of patients with T2DM [17], [18]. Insulin resistance is key in the pathophysiology of NAFLD.[19] Numerous studies have demonstrated that the presence of insulin resistance and/or diabetes is a risk factor for the development of NASH and fibrosis progression. [20]–[24]

In patients with dyslipidaemia, the prevalence of NAFLD is estimated to be over 50%; in particular, in those with the lowest total cholesterol to HDL-cholesterol and TG to HDL-cholesterol ratios, the prevalence rate was 33%, although in the group with the highest ratios it was 78%. [25]

Also, older age has been described as an independent risk factor for hepatic steatosis and progression to fibrosis and cirrhosis, probably due to the higher prevalence of metabolic comorbidities but also mitochondrial dysfunction.[26], [27] The Rotterdam study demonstrated a correlation between the increase of liver stiffness

measurements (LSM) and increasing age, with LSM being also strongly associated with steatosis and T2DM. [22]

Finally, genetic factors and ethnicity have been related to a greater risk for NAFLD; the highest prevalence of NAFLD was observed in Hispanic populations [28] while several genetic modifiers such as the PNPLA3 single nucleotide polymorphism have been identified, but a minority have been robustly validated[1].

4. FIBROSIS PROGRESSION

Although only 5-10% of patients who have NAFLD develop NASH, this is one of the key drivers of fibrosis. Whereas the presence of NASH per se is not associated with the development of liver-related mortality, advanced fibrosis, scored either semi-quantitatively or measured quantitatively with collagen proportionate area (CPA), is significantly correlated with a worse long-term outcome [29], [30]. The progression of liver fibrosis in the context of NASH is not fully understood due to the limited amount of high-quality prospective data. Advanced fibrosis is the most significant predictor of death from liver-related disease [30], and the presence of fibrosis is directly linked with the risk of liver-related events [24]. A schematic representation of the evolution of NAFLD is illustrated in Figure 1. The progression of steatohepatitis and fibrosis in patient cohorts by utilizing paired liver biopsies was reported by at least 12 studies. The conclusion was that a third of patients with NAFLD and NASH have progressive fibrosis and 20% will have regression over an average follow-up between 2.2 and 13.8 years.[31] The main criticism for such studies is that repeat biopsies were performed as a response to physicians' concerns for disease progression rather than per protocol, therefore the rate of disease progression in unselected patients is likely significantly lower than what is reported in such studies.

Singh and colleagues evaluated the rate of histological fibrosis progression in adults with NAFLD finding that the progression differed depending on the severity of baseline fibrosis: it was slower in patients with more indolent disease at the outset, and more rapid in patients with NASH at baseline. Notably, rates of progression were still slow; specifically, the time taken to advance by one stage of liver fibrosis was 7 years in fast-progressing disease versus 14 years in slow-progressing disease. Arterial hypertension was the only factor independently associated with fibrosis progression in

that meta-analysis [32]. The reduction in transaminase levels was correlated with the decrease of features of steatosis, inflammation, and ballooning [4].

The main risk factors for fibrosis progression in other cohorts are a combination of metabolic factors, such as diabetes, obesity, and hypertension, as well as common genetic polymorphisms in the PNPLA3 and TM6SF2 genes, increasing the risk of developing cirrhosis and HCC. [31]

The risk of Hepatocellular Carcinoma (HCC) in patients with NAFLD was estimated to be increased in all stages of the disease, even in non-cirrhotic patients. Specifically, a more than 2.5-fold increased risk of HCC was estimated in non-cirrhotic NASH patients compared to other aetiologies of non-cirrhotic chronic liver disease [33].

5. A HEALTH CARE CHALLENGE

As described above, NAFLD is dramatically prevalent with prospects of further increase, despite being non-progressive in the majority of cases. The role of the general practitioners (GPs) is therefore key both in managing the majority of these patients in primary care but also in selecting those at risk for advanced liver disease for referral in secondary care. At the moment, a substantive number of GPs are not confident in managing NAFLD; for this reason education and guidelines of the management of NAFLD in primary care are needed, as highlighted in various papers of the last years.[34]–[36] Frequently liver disease is not considered as a primary care priority. In consequence NAFLD management in primary care is inadequate due to a lack of definite direction, a perception of futility due to lack of licensed pharmacological treatment and uncertainty due to lack of clinical pathways.[52]

Generally, the triggers of a diagnosis of NAFLD are abnormal liver blood tests (LFTs) results or the incidental detection of steatosis on imaging performed for an unrelated indication. The above should lead to the exclusion of other causes of liver disease through a liver screen[37], an evaluation of metabolic comorbidities and a comprehensive alcohol history. Patients with abnormal LFTs without clinical risks, signs or symptoms of liver disease are a challenge for primary care practitioners. Notably, the large UK prospective study of Skelly et al demonstrated that in a group of patients referred to secondary care with unexplained abnormal LFTs, after excluding patients with known liver disease, 66% had a diagnosis of NAFLD/NASH, and, in particular, 18% of NASH patients' biopsy had significant fibrosis. In the analysis of Armstrong et al, the commonest cause of incidental LFT abnormalities in primary care was NAFLD, diagnosed in 26.4% of the cases, of whom 7.6% have advanced fibrosis suggested by the presence of a high NFS. [38]

However, normal LFTs do not rule out fatty liver and/or NASH. Indeed, the entire histologic spectrum of NAFLD can be observed in individuals with normal LFTs , without significant difference from those with elevated ALT levels.[39] Portillo-Sanchez et al. demonstrated that half of a population with diabetes and normal LFTs had NAFLD as diagnosed with the use of 1H-MRS, with a higher prevalence in overweight and obese patients. Moreover, the prevalence of NASH between NAFLD patients, diagnosed by biopsy, was 56%. [40]

Therefore, LFTs cannot be used to diagnose NAFLD or differentiate those who have NASH and/or fibrosis. The gold standard to differentiate NAFLD from NASH and accurately stage fibrosis is a liver biopsy. However, it is impossible to perform a liver biopsy in every NAFLD patient, because of cost and procedure-related morbidity [41], therefore this is reserved in cases of uncertainty in diagnosis or if advanced liver disease is suspected. [1], [42]. Several non-invasive fibrosis tests have been developed and can be used for staging fibrosis, particularly to rule out patients who do not have advanced fibrosis. These tests have greatly reduced the need for liver biopsies and should be used for the initial assessment of patients with NAFLD. Early risk stratification should be a focal point in the management of NAFLD, in order to detect patients with advanced fibrosis or cirrhosis and offer interventions and surveillance that could prevent further progression.

6. SCREENING FOR NAFLD IN PRIMARY CARE

Screening programmes are designed to detect early signs of disease in selected populations and then to provide a reliable method of referral for further treatment. In order for a screening programme to be considered for widespread use, it must be acceptably accurate, affordable and designed to test for a disease where earlier detection and intervention would be of benefit to the patient.

Systematic screening for NAFLD is not recommended by major national or international learned societies (European Association for the Study of the Liver (EASL)[1], American Association for the Study of Liver Diseases (AASLD) [43], National Institute for Health and Clinical Excellence (NICE) [42], Italian Association for the Study of the Liver (AISF) [44], British Society of Gastroenterology (BSG) [37], Asia-Pacific guideline [45], Belgian Association for the Study of the Liver (BASL) [46], and Spanish Association for the Study of the Liver (AEEH) [47]) because of the high direct and indirect costs of testing, the low predictive value of non-invasive tests and the lack of effective treatments. On the other hand, screening in groups deemed at high risk remains a contentious issue, due to the lack of data on disease progression and long-term outcomes in unselected populations, the absence of an optimal screening test and effective disease-specific therapies, as well as insufficient data on the cost-effectiveness of the approach.

The American Association for the Study of Liver Diseases guidelines emphasizes that there is no evidence of cost-effectiveness to support screening for NAFLD in adults, even in patients with metabolic risk factors, instead suggesting a concept of “vigilance” for chronic liver disease in patients with type 2 diabetes [43].

On the other side, other guidelines recommend that screening for NAFLD should be part of a routine workup in particular “high-risk” groups, however, the definitions of

“high risk” group could be slightly different, as showed in Table 1. EASL defines as high risk subjects with obesity or metabolic syndrome [1], NICE those who have type 2 diabetes or metabolic syndrome [42], the Asia-Pacific guideline those with type 2 diabetes and obesity [45], the Belgian Association for the Study of the Liver the presence of metabolic syndrome and its components or patients with a history of ischemic CVD[46], and Spanish Association for the Study of the Liver those with obesity, type 2 diabetes or metabolic syndrome[47].

Abdominal ultrasonography (US) remains the recommended first-line imaging modality for the diagnosis of NAFLD in clinical practice, due to its broad availability and low cost; moreover, it provides additional information about the hepatobiliary system, but can only detect moderate or severe steatosis. [1]. Regarding the disadvantages, US is observer-dependent, has limited sensitivity and does not reliably detect steatosis when <20% [38], [39] or in individuals with high body mass index (BMI) (>40 kg/m2) [40]. Magnetic resonance imaging and proton magnetic resonance spectroscopy are able to detect the hepatic fat content, especially for mild disease (<30% steatosis), avoiding exposure to radiation.[48] Magnetic resonance spectroscopy (MRS) is a safe, non-invasive and accurate method for hepatic fat quantification with high sensitivity and specificity, however due to its low availability and limited clinical application remains primarily a research tool [49], [50]. The magnetic resonance imaging–estimated proton density fat fraction (MRI-PDFF) is an objective and quantitative indicator that allows fat mapping of the entire liver but also has a higher sensitivity than histology in detecting changes in hepatic fat content [51]. Controlled attenuation parameter (CAP) is a non-invasive examination, that using the fat effects on the ultrasound propagation, measures the underlying steatosis grades using the ultrasonic signals acquired by the FbroScan.[52] The diagnostic accuracy

is higher for hepatic steatosis of S1 and S2 than for the ≥S3 steatosis; specifically, the sensitivity of CAP was 87% and 85% in detecting mild and moderate steatosis, dropping to 76% for the detection of severe steatosis. Therefore, CAP may not be a reliable test for the detection of moderate to severe steatosis. [53], [54]

BASL recommends the use of Fatty Liver Index (FLI) and NAFLD Liver Fat score for the diagnosis of steatosis in large-scale epidemiological studies whenever imaging tools are not available.[46] The FLI score is calculated using body mass index (BMI), waist circumference, triglycerides and gamma-glutamyltransferase (GGT); scores above 60 (Sn 61; Sp 86) indicates the presence of steatosis, whereas no steatosis is expected if the score is below 30 (Sn 87; Sp 64)[55]. The NAFLD Liver Fat Score is calculated by a formula that includes the presence of metabolic syndrome, type II diabetes, fasting serum insulin, AST and AST/ALT ratio; the two cut-offs to define the risk of steatosis are -1.413 and 1.257 (Sp 95; Sn 95).

Irrespective of the method used, the diagnosis of steatosis even in high-risk groups, is of limited prognostic significance and not cost-effective. Moreover, a false negative result could lead to false reassurance and prevent further testing in people at risk of liver disease. Therefore, on balance, the AASLD guidance on screening is in our opinion the preferred option at the moment.

7. NON-INVASIVE LIVER FIBROSIS TESTS

Several non-invasive diagnostic strategies have been already proposed as alternatives to liver biopsy in patients with NAFLD, with various levels of diagnostic accuracy. The non-invasive liver fibrosis tests can be broadly divided into three categories: simple or indirect serum markers, direct serum markers and imaging modalities.

Routine laboratory tests (such as platelet count or transaminases) combined with patient demographics potentially linked to liver fibrosis, such as age or diabetes, are categorized as indirect serum markers or class II biomarkers. [56]

Usually, such tests have a low cut-off with high sensitivity (to rule out the presence of advanced fibrosis) and a high cut-off with high specificity (to diagnose the presence of advanced fibrosis) which can be used interchangeably depending on the clinical scenario and the disease prevalence.

The NAFLD fibrosis score (consisting of age, hyperglycemia, BMI, platelet count, albumin, and AST/ALT ratio) and the FIB-4 index (consisting of age, AST, ALT, and platelet count) are the best performing and validated indices in NAFLD. Of the two, FIB-4 has shown better diagnostic accuracy in head-to-head studies and is easier to calculate. [57], [58]

The products of extracellular matrix synthesis or degradation, and the enzymes that regulate their production or modification (e.g. hyaluronic acid, collagenases and their inhibitors, and profibrotic cytokines) are classified as direct or class I serum markers. The limitations of these markers are the lack of sensitivity in the mild stages of liver fibrosis, the cost and the low specificity in patients with extrahepatic fibrotic conditions. [56]

The enhanced liver fibrosis (ELF) test is a patented algorithm based three serum markers: hyaluronic acid (HA), amino-terminal propeptide of type III procollagen (PIIINP), and tissue inhibitor of metalloproteinase 1 (TIMP- 1). The ELF score has good diagnostic accuracy for advanced fibrosis (stages 3-4) with an AUC of 0.9, but the AUCs for moderate and mild fibrosis are 0.82 and 0.76 respectively. [59] Other patented tests include the Fibrotest, the Fibrometer and the Hepascore. [41]

Imaging modalities measure the elasticity and/or stiffness of the liver tissue using US or MR techniques. [58]

Vibration-controlled transient elastography (VCTE) is a one-dimensional (1D) US-based technique performed with the FibroScan system (Echosens, Paris, France), that has gained popularity in secondary care setting as well as in community health services, because the measurements can be easily performed at the bedside or in the outpatients' clinic with immediate results and good reproducibility. [60] In a novel prospective multicentre study by Eddowes et al, the vibration-controlled transient elastography (VCTE) correlated significantly with liver histology, and notably, only fibrosis stage was independently related to the liver stiffness measure without probe type or any other histological parameters influencing the results. [53]

Recently, we have shown that only the combination of existing NITs can substitute liver biopsy for the diagnosis of cirrhosis, as none of these tests has sufficient diagnostic accuracy as stand-alone test.[61]

Radiologic and serum non-invasive markers have equally high negative predictive values for ruling out advanced fibrosis, thus, given the low prevalence of advanced fibrosis in unselected patients with NAFLD such tests or their combination are useful to exclude the presence of advanced fibrosis and can be used to guide referrals for dedicated hepatology input. Moreover, non-invasive fibrosis assessment has the

possibility of being repeated in time, so it should not only identify NAFLD among patients with metabolic risk factors but also monitor the disease progression and treatment response, determining patients with the worst prognosis. [59] The most commonly used non-invasive fibrosis tests in NAFLD are described in Table 2.

8. STRATEGIES FOR STRATIFYING PATIENTS WITH NAFLD

The optimal strategy for stratifying NAFLD patients has not been yet established. The different proposals of existing guidelines are summarised in Table 1.

In 2015, despite evidence of acceptable diagnostic accuracy with non-invasive assessment with NAFLD fibrosis score, ELF and FibroScan, the Japanese Society of Gastroenterology recommended in its guidelines to establish the diagnosis of NAFLD or NASH by histology, after ruling out other liver diseases and alcohol consumption. [62]

In the EASL clinical practice guidelines, after the diagnosis of steatosis with the US and LFTs, non-invasive scores (NFS and FIB4) and transient elastography are recommended to differentiate patients at high-risk of advanced fibrosis who need to be referred to secondary care from patients at low-risk that can be followed up in primary care with a follow reassessment every 2-3 years [1]. Since the prevalence of advanced fibrosis in unselected population is low, it is expected that 60% of patients will have low scores and will not need further assessment. [61]

Even though the AISF guidelines acknowledges the diagnostic flow-chart of the EASL guidelines, a specific pathway to spare patients from undergoing liver biopsy is not proposed; instead, imaging techniques (e.g. ultrasonography-based transient elastography (Fibroscan), 2D acoustic radiation force impulse imaging or MR-elastography) and/or serum biomarkers (e.g. the NAFLD fibrosis score, the FIB-4, the FibroTest, the Fibrometer, and the ELF score) have been illustrated as a first step to stratify the risk of liver fibrosis, without a specific preference. [42]. Similarly, the Asia–Pacific Working Party guideline commented on the reasonable diagnostic accuracy of some serum tests and physical tests, without a specific preference, but underlining

that the data from the combination of serum tests and physical tools can yield more reliable data than that afforded by either method alone. [45]

The AASLD guideline and the AEEH guidelines recommend the use of NFS or FIB-4 or vibration controlled transient elastography to stratify the risk of advanced fibrosis with a high index of suspicion for NAFLD and NASH; the frequency of the determinations has been not defined, however, the AEEH guidelines recommend to measure liver stiffness annually in patients with advanced fibrosis (≥F3) and every three years in patients with milder disease. Liver biopsy should be considered when the presence and/or severity of the chronic liver disease cannot be excluded. However, no diagnostic algorithms or follow up strategies are provided. [43]

Regarding the NICE guidelines, the ELF blood test is recommended to screen for advanced fibrosis in every patient with NAFLD; patients with scores higher than 10.51 should be referred to a hepatology service, while patients with scores below 10.51 should be monitored every 3 years in primary care, without interim tests. [42]

The recent British Society for Gastroenterology guidance on the management of abnormal LFTs recommend a 2-tier approach to detect the presence of advanced fibrosis: the first step using either FIB-4 and NAFLD fibrosis score, as inexpensive first screen in a combined cut-off approach, with further testing patients with indeterminate scores using more sensitive and specific tests, namely enhanced liver fibrosis (ELF) test or FibroScan. [63]

The combinations of biomarker scores were also proposed in the Belgian guidelines to confer additional diagnostic accuracy and potentially spare several diagnostic liver biopsies, proposing an algorithm based on the combination of FLI, FIB-4 and the NFS. When both the fibrosis scores are under the low cut-off (NFS < -1.455; FIB-4 < 1.30), the follow-up depends on the FLI value, that can be under 30, between 30 and 60 or

over 60, with a respective follow-up at 2 years, 1 year or 6 months. If one of the fibrosis score is below the low cut-off (NFS < -1.455; FIB-4 < 1.30) or both are in the grey area (NFS: between -1.455 and 0.67; FIB-4: between 1.30 and 2.67), independently to the FLI score, lifestyle modification and retest in 6 months are recommended. Finally, further hepatological investigations are recommended when one or both the fibrosis scores are over the high cut-off (NFS > 0.67; FIB-4 > 2.67), independently to the FLI score.

Unfortunately, evidence supporting the application of non-invasive tests in the community setting is little due to the lack of studies about the use of non-invasive assessment for the diagnosis of fibrosis. Harris et al. analysed in a systematic review the use of non-invasive tests to screen for the risk of liver disease in a general population setting.[64] The prevalence of fibrosis in the general population in ten studies ranged between 2% and 19%, while advanced fibrosis was estimated at 0.9% by FibroTest (≥0.59) in a study of Zelber-Sagi et al [65], and at 2.6%, by transient elastography (≥9.6 kPa) in a study of Wong et al. [66]. The prevalence of advanced fibrosis in patients at risk of NAFLD was determined in 4 studies with a range from 0% to 27.9% [64]; notably, the study of Wong et al, using several non-invasive test, obtained the lower value 0% with NFS (≥0.676) and APRI (≥1.5) whereas the prevalence was increased to 3.7% with the use of transient elastography (≥9.6 kPa) and to 12.1% with the use of AST/ALT ratio (≥1). [66]

We recently published the results of a real-world pathway to triage patients with NAFLD in primary care using blood tests on the basis of their risk of advanced fibrosis. The Camden and Islington NAFLD Pathway consisted of a 2-step non-invasive test assessment, starting with the calculation of the FIB-4 score to divide the population in low-risk (FIB-4<1.30), high-risk of advanced fibrosis (FIB-4 >3.25) or patients with

indeterminate results (FIB-4 between 1.30-3.25). Patients at low risk of advanced fibrosis remained in primary care with particular care management of cardiovascular risk factors and patients at high risk were referral to secondary care for specialist assessment. Patients with indeterminate results had second tier non-invasive tesing with an ELF test. Consequently, the referral to secondary care was recommended only in patients in those with an ELF score above 9.5. Adherence to the pathway resulted in the detection of 5 times more cases of advanced fibrosis and cirrhosis than standard of care, also reducing unnecessary referrals to secondary care by 81%. Moreover, the number of referrals required to detect one case of advanced fibrosis was 3.4 using the pathway compared to 12.6 using standard care.[63]

Another successful pathway was described by Harman et al., who used a BARD score <2 (calculated using BMI, AST:ALT and T2D), to rule out significant liver fibrosis in subjects with risk factors, such as hazardous alcohol use and/or type 2 diabetes. Patients with a BARD score ≥2 were tested using transient elastography in general practice to detect advanced fibrosis or cirrhosis. Liver stiffness values greater than 8kP were observed in 25.6% of patients and 2.9% had cirrhosis. Using this testing pathway, the diagnosis of cirrhosis was doubled compared to standard of care in the participating general practices. The majority of identified patients with cirrhosis had type 2 diabetes and obesity as risk factors, while the risk of cirrhosis was higher in those with multiple risk factors (hazardous alcohol use, obesity, and type 2 diabetes).[67]

Strategies to stratify patients on the risk of advanced fibrosis, regulate the number of referrals to secondary services and the costs for the healthcare system are crucial, in consideration of the rising prevalence of NAFLD along with the awareness of the community. The financial impact of introducing non-invasive tests into primary care

was analyzed in several papers, unequivocally showing that compared to standard of care these strategies reduce the referral rate from primary care to hospital and are also cost-efficient.

A recent analysis by Crossan compared three different scenarios: a direct referral to secondary care, a referral after a two-steps non-invasive screening in primary care and referral of patients with advanced fibrosis only after confirmation with a liver biopsy. The two-tier approach (FIB-4 as the first step followed by ELF, Fibroscan or FibroTest if FIB-4 value was indeterminate) reduced the referral rate to approximately 10% compared to the referral rate of 29% using only FIB-4. Furthermore, this pathway decreased the cost per patient by 40% with an accurate selection of the patients at a higher risk of advanced fibrosis [58].

A novel analysis by Srivastava compared the standard of care to two-tier stratification approaches, such as FIB-4 and ELF or FIB-4 and FibroScan, or one-tier approaches, such as ELF or FibroScan alone. The detection of advanced fibrosis is increased in all scenarios. TE alone is the most clinically effective strategy in the detection of ≥F3 fibrosis whereas the most cost-effectivene approach is the combination of FIB-4 and ELF score. Focusing on the cost-per-case of advanced fibrosis, all scenarios were more cost efficient than the standard of care (£25,543), while the combination of FIB-4 and ELF offers the greatest cost-saving (£8.932).[68]

A proposed pathway for stratifying patients with NAFLD is illustrated in figure 2. The purpose is to identify the patients who are at high risk of advanced fibrosis and would benefit from a secondary care referral and reassure those who do not meet these criteria and can be managed in primary care.

3.7 MANAGEMENT IN PRIMARY CARE

The target of primary care physicians in managing patients with NAFLD should be the treatment of metabolic comorbidities in order to reduce the cardiovascular risk and also to prevent future progression of the hepatic component of the disease. Patients should be encouraged to lose weight through lifestyle changes, while type II diabetes, hyperlipidaemia and hypertension should be treated according to existing guidelines on these conditions with strict adherence to therapeutic targets. Overweight/obese patients should be supported with structured programs aimed at lifestyle changes though healthy diet and habitual physical activity, as loss of more than 5% of the body weight is associated with a 58% chance of resolution of NASH, while loss of 10% of body weight is associated with a 90% chance of NASH resolution of 90% and a 45% chance of a one stage fibrosis improvement [69].Regarding pharmacotherapy, currently, no drugs have been approved for the treatment of NASH by the US Food and Drug Administration or by the European Medicines Agency. However, some drugs could be preferred for the treatment of metabolic comorbidities, because of a potential benefit in NAFLD. A stepwise approach is recommended in T2DM; metformin is the first line of therapy, despite no convincing evidence of histological efficacy.[70] The add on choice depends on the patients BMI and would be pioglitazone if the BMI is under 30 kg/m^2, because of its correlation with increased insulin sensitivity, a decreased of the aminotransferases [65] and, in the PIVENS trial, an improvement in all histological features (except for fibrosis) [66]. Otherwise, if BMI is over 30 kg/m^2 the use of GLP-1 agonists is advisable, considering their positive effect on body weight and potentially beneficial effect on histology.[71] The prescription of statins, in patients with eligible cardiovascular risk scores, is indicated and safe from a liver point of view; moreover, statins could improve LFTs and reduce vascular comorbidity [72]. In

hypertensive patients, angiotensin II blocker was associated with amelioration of insulin resistance and anti-fibrotic effects in the liver, in small randomized trials [73], [74].

9. CONCLUSIONS

The growing burden of obesity is a deeply concerning public health issue and it has resulted in the global increase in the prevalence of NAFLD, that is over a quarter of the general population. The number of liver transplants for this disease is exceeding other liver aetiologies.

In this scenario, a key role is played by primary care practitioners, because they could evaluate the risk factors of NAFLD in a large proportion of the population and manage referrals to secondary care. Indeed, the first step in the evaluation of such patients is crucial because not only has an impact on the possible evolution of the disease but also health expenditure. In other words, awareness and education about NAFLD are indispensable to recognize early signs of progressive liver disease, to classify the patient risk and to refer patients at high risk, thus decreasing inappropriate referrals and reducing the progression and mortality of liver disease.

The remaining percentage of NAFLD patients at low risk demands a rigorous control of their metabolic comorbidities, as their cardiovascular risk exceeds the risk of death from liver diseases. In particular, a healthy lifestyle and optimal management of their metabolic syndrome components are indicated.

For these reasons an integrated management plan between primary care and secondary care is indispensable, to define pathways of testing for advanced fibrosis and subsequent secondary care referrals [5].The use of an integrated pathway between primary and secondary care for the stratification of NAFLD patients has only been evaluated studied in a study we conducted [63]. Further studies are required to confirm the applicability and efficacy of NAFLD pathways.

LIST OF ABBREVIATIONS

AASLD:	American Association for the Study of Liver Diseases
AEEH:	Spanish Association for the Study of the Liver
AISF:	Italian Association for the Study of the Liver
LFTs:	Liver blood tests
ALT:	Alanine Aminotransferase
AST:	Aspartate Aminotransferase
BASL:	Belgian Association for the Study of the Liver
BMI:	body-mass index
BSG:	British Society of Gastroenterology
CPA:	Collagen Proportionate Area
CAP:	Controlled attenuation parameter
EASL:	European Association for the Study of the Liver
FIB-4:	Fibrosis-4 score
FLI:	Fatty Liver Index
GPs:	General Practitioner
HCC:	Hepatocellular Carcinoma
H-MRS:	Proton Magnetic Resonance Spectroscopy
JSGE:	Japanese Society of Gastroenterology;
LFTs:	Liver Functional Tests
LSM:	Liver Stiffness Measurements
MetS:	Metabolic Syndrome
MRE:	Magnetic Resonance Elastography
MRI-PDFF:	Magnetic Resonance Imaging-Proton Density Fat Fraction
NAFLD:	Non-alcoholic Fatty Liver Disease

NASH:	Non-Alcoholic Steatohepatitis
NFS:	NAFLD Fibrosis Score
NICE:	National Institute for Health and Clinical Excellence
NITs:	Non-invasive tests
OSA:	Obstructive Sleep Apnoea
PIIINP:	Amino-Terminal Propeptide of Type III Collagen
PLT:	Platelet Count
Sn:	Sensitivity
Sp:	Specifity
T2DM:	Type 2 Diabetes Mellitus
TIMP-1:	Metalloproteinase Inhibitor 1
US:	Ultrasonography
VCTE:	vibration-controlled transient elastography

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TABLE 1: Recommendations from NAFLD guidelines of national and international learned societies.

	Screening in general population	**Screening in high risk population**	**Definition of high risk**	**Non- invasive Assessment of advanced fibrosis**	**Follow-up**
JSGE 2015 [62]	Not-specified	No	Not specified	NFS and ELF transient elastography	No recommendation provided
EASL 2016 [1]	No	Yes	Obesity MetS	Markers of fibrosis (NFS, FIB-4, ELF or FibroTest) upon diagnosis. If inconclusive, perform transient elastography	Negative markers: reassessment every 2 -3 years; Fibrosis or abnormal liver enzyme: reassessment every year; Cirrhosis: surveillance every 6 months.
NICE 2016 [42]	No	Yes	T2DM MetS	ELF	ELF < 10.51: reassessment every 3yrs ELF > 10.51: liver biopsy
AISF 2017 [44]	No	Yes	Not specified	Fibroscan, 2D acoustic radiation force impulse imaging or MR-elastography and/or serum biomarkers NAFLD fibrosis score, the FIB-4, the FibroTest, the Fibrometer, and the Enhanced Liver Fibrosis (ELF)	Negative markers reassessment every 2 years Fibrosis or abnormal liver enzyme reassess every year Cirrhosis surveillance every 6 months

BSG 2017 [37]	No	Not specified	Not specified	Markers of fibrosis (NFS or FIB-4) upon diagnosis. If inconclusive: ELF or FibroScan/ ARFI	No recommendation provided
Asia–Pacific Working Party 2018 [45]	No	Yes	T2DM Obesity,	Combination of serum tests and imaging tools (no specification about the preferred tests)	No recommendation provided
BASL 2018 [46]	No	Yes	T2DM Obesity, MetS patients with a history of ischemic CVD	Combination of the FLI, FIB-4 and the NFS	NFS (> 0.67) and/or FIB-4 (> 2.67), independently by FLI → referral for further hepatological investigation NFS (< -1.455) or FIB-4 (< 1.30) or NFS (>-1.455; < 0.67) and FIB-4 (> 1.30;<2.67), independently by FLI → lifestyle modification and repetition of fibrosis marker after 6 months NFS < -1.455 and FIB-4 < 1.30: - FLI < 30 → revaluation every 2 years - FLI > 30;<60 → revaluated again after 1 year of intensive lifestyle modifications

					- FLI >60 → revaluated again after 6 months of intensive lifestyle modifications
AEEH 2018 [47]	No	Yes	T2DM Obesity, MetS	NFS and FIB-4 FibroScan	Advanced stages (≥F3): FibroScan annually Initial stage: FibroScan every three years
AALSD 2018 [43]	No	No	T2DM	NFS and FIB-4 ELF FibroScan	No recommendation provided

AASLD: American Association for the Study of Liver Diseases; AEEH: Asociación Española para el Estudio del Hígado [Spanish Association for the Study of the Liver]; AISF: Associazione Italiana Per Lo Studio Del Fegato [Italian Association for the Study of the Liver]; ARFI : acoustic radiation force impulse elastography; BASL: Belgian Association for the Study of the Liver; BSG: British Society of Gastroenterology; EASL:Associazione europea per lo studio del Fegato; ELF: Enhanced Liver Fibrosis test; FIB-4:Fibrosis-4, FLI: Fatty Liver Index, JSGE: Japanese Society of Gastroenterology; MetS: Metabolic syndrome; NFS: NAFLD Fibrosis Score; NICE: national institute for health and clinical excellence; T2DM: type 2 diabetes mellitus.

TABLE 2: Non-invasive fibrosis tests commonly recommended for advanced fibrosis (> F3) in patients with non-alcoholic fatty liver disease (NAFLD)

	COMPONENT	CUT OFF	CORRELATED FIBROSIS SEVERITY	SENSITIVITY	SPECIFITY	NPV	RELATIVE COST [68]
NFS [75]	Age, BMI, T2DM, AST, PLT, Albumin	- 1.455 (low cut-off)	<F3	0.82	0.77	0.93	Negligible
		- 0.676 (high cut-off)	≥F3	0.51	0.98	0.85	
FIB-4 [58]	AST, ALT, age, PLT	1.30 (low cut off)	<F3	0.74	0.71	0.73	Negligible
		2.67 (high cut-off)	≥F3	0.34	0.98	0.59	
ELF test [41]	Hyaluronic acid, PIIINP, TIMP-1	10.35	≥F3	0.80	0.90	0.99	£42
FibroScan [41]	IMMAGING MODALITY	8 Kpa	≥F3	0.82	0.84	0.99	£43

The negative predictive value (NPV) is based on a prevalence of advanced fibrosis of 5%. (NFS: NAFLD Fibrosis Score. BMI: body-mass index. AST: aspartate aminotransferase. ALT: alanine aminotransferase. PLT: platelet count. ELF: Enhanced Liver Fibrosis test. PIIINP: amino-terminal propeptide of type III collagen. TIMP-1: metalloproteinase inhibitor 1)

KEY POINTS:

1. The global prevalence of NAFLD is estimated exceed 25% of the general population, in progressive growth; the highest rates are reported from South America and the Middle East, followed by Asia, the USA, and Europe. A strong association between NAFLD and MetS has been established.
2. The prognosis of NAFLD is generally benign in the absence of fibrosis, but liver fibrosis rapidly progresses in 30% of the cases and lead to cirrhosis and/or HCC. Advanced fibrosis is the most significant predictor of death from liver-related disease.
3. GPs has the key role to recognize screen the population between who is at high-risk and needs a referral to the second level of cure in patients and who is a low-risk and needs only of a careful management of metabolic comorbidity to reduce the cardiovascular risk.
4. Algorithms based on the combination of existing NITs could be used to stratify the risk of the NAFLD population and to regulate access to secondary care, with a positive cost-effect.

FIGURE 1: Natural history of NAFLD.

Abbreviations: NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis;

HCC, hepatocellular carcinoma

FIGURE 2: Step-wise algorithm for testing patients with NAFLD for the presence of advanced fibrosis

FIGURE 3: Management of NAFLD