12 Diagnostic Algorithm for the Identification of NAFLD in Primary Care

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Abbreviations

AASLD	American Association for the study of liver diseases
APASL	The Asian Pacific Association for the Study of the Liver
EASL	European Association for the Study of the Liver
GP	General Practitioner
MetS	Metabolic syndrome
NAFLD FS	NAFLD fibrosis score
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
T2DM	Type 2-diabetes mellitus
TE	Transitory elastography

Nonalcoholic fatty liver disease (NAFLD) is extremely frequent. According to Younossi et al., about 25% of the world population has NAFLD [1], with large variations among continents and countries in prevalence, with Western countries having the highest prevalence and African countries the lowest. However, among the large number of individuals with NAFLD only a minority has severe liver disease. This was well demonstrated in an Asian study, where among 922 subjects, NAFLD, based on proton magnetic resonance spectroscopy, was observed in 27.3%, while advanced fibrosis, based on liver stiffness measurement, was found in only 3.7% [2].

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E. Bugianesi (ed.), *Non-Alcoholic Fatty Liver Disease*,
https://doi.org/10.1007/978-3-319-95828-6_12

The majority of NAFLD patients are probably being followed in primary care and only a minority is referred to specialist care. In a large study from UK, it was found that NAFLD is the commonest cause of incidental LFT abnormalities in primary care (26.4%), of whom 7.6% have advanced fibrosis as calculated by the NAFLD fibrosis score (NFS) [3].

In this chapter, it will be discussed to which extent the identification and referral of these patients is justified, and what methodology is more useful to achieve it.

12.1 Relevance and Screening for NAFLD in Primary Care

A major point of controversy relates to the need of population screening for NAFLD. According to Wilson and Jungner classic screening criteria (WHO 1968), one of the major requirements for public health screening to be accepted is that there should be an accepted treatment for patients with the recognized disease [4]. In fact, the absence of an effective treatment is probably the major factor against screening for NAFLD. Nonetheless, there is recent evidence of the impressive effects of life-style interventions accompanied by significant weight loss in the improvement or resolution of steatosis/steatohepatitis [5, 6]. Consequently, there may be a role for screening, in order to recommend these lifestyle changes that may simultaneously reduce the increased risk of cardiovascular disease as well as cancers in these patients.

There is general agreement from the Hepatology scientific societies that the screening of the general population is not cost-effective [7–9]. There is however disagreement regarding the screening of particular groups. In fact, the European Association for the Study of the Liver (EASL) states that individuals with obesity or metabolic syndrome should be screened for NAFLD by liver enzymes and/or ultrasound as part of their routine workup [7]. The same guidelines indicate that high-risk individuals, such as those older than 50 years, with type 2 diabetes mellitus (T2DM) or metabolic syndrome (MetS), should undergo evaluation for the presence of advanced liver disease (nonalcoholic steatohepatitis—NASH) [7]. On the other hand, the 2018 American Association for the study of liver diseases (AASLD) guidelines consider that even in high-risk groups from primary care, diabetes or obesity clinics, routine screening for NAFLD is not advisable, mostly due to the doubts regarding the treatment options and diagnostic tests as well as the lack of knowledge regarding long-term benefits and cost-effectiveness [8]. However, it is admitted that there should be a high index of suspicion for the presence of NAFLD and NASH in T2DM, and that it may be useful to identify those that are at low- or high risk for advanced fibrosis [8].

The Asian Pacific Association for the Study of the Liver (APASL) Working Party NAFLD 2017 guidelines suggest that screening for NAFLD may be considered in risk groups such as patients with T2DM and obesity, mostly reasoning that in these subgroups the probability of having severe disease is much higher that in those with NAFLD from the general population [9].

Actually, in primary care, it was found that in patients with T2DM, the prevalence of NAFLD (defined as MRI-PDFF ≥5%) and advanced fibrosis (defined as MRE ≥3.6 kPa) was 65% and 7.1%, respectively [10]. In another study, also in T2DM, and using transitory elastography (TE), among 1918 patients, the proportion of patients with NAFLD and those with advanced fibrosis was 73% and 18%, respectively [11]. Also, among obese subjects the prevalence of NAFLD, based on proton magnetic resonance spectroscopy, and advanced fibrosis, based on liver stiffness measurement, was 61% and 19%, respectively [12].

Nonetheless, a cost-effective analysis using a Markov model found screening for NASH in individuals with diabetes although improving liver-related outcomes was not cost-effective, due to side effects of therapy [13].

12.2 Methods for NAFLD Identification

As shown in the previous section, there is no role for actively searching for NAFLD in the general population.

However, there is evidence of lack of recognition of NAFLD among general practitioners (GPs) in UK, as in the USA [14, 15]. In fact, Blais et al. found that the majority of patients in a primary care unit were not being recognized and evaluated, although all the patients identified had evidence of the metabolic syndrome. Only 3% of patients at a high risk of advanced fibrosis had been referred to a specialist consultation [15]. There seems to exist a gap in the GPs knowledge and cognizance of relevant practice guidelines. It has been reported in one study from the USA that over 40% of GP surveyed were not familiar with clinical published guidelines related with NAFLD management [16]. In general, GPs tend to give excessive attention to elevated aminotransferases while disregarding well-accepted predictors of more serious disease, such as older age, elevated body mass index (BMI), presence of diabetes, hypertension, or hypertriglyceridemia [17], thus overlooking the patients who are in fact in higher risk of more serious disease [15].

Furthermore, it was found that a small percentage of these patients with NAFLD, and no clinical manifestations, had advanced fibrosis, and would benefit from screening for life-threatening complications such as hepatocellular carcinoma or variceal bleeding.

In patients presenting with significant metabolic risk factors such as the existence of diabetes or obesity, in order to identify the presence of NAFLD the best method is liver ultrasound (US). In fact, sensitivity and specificity of ultrasound was found as good as other imaging techniques, such as computed tomography (CT) or magnetic resonance imaging (MRI) [18]. Since US has a low cost and it is safe and accessible, it is likely the imaging technique of choice for screening for fatty liver in clinical and population settings [18]. Furthermore, it can simultaneously evaluate the presence of biliary disease or liver metastases. The major drawback of liver ultrasound is that it does not quantify the degree of fibrosis that is the major predictor of end-stage liver disease, hepatocellular carcinoma, and survival [19, 20].

Table 12.1 Other causes of steatosis

Concomitant or alternative causes of steatosis	Tests for evaluation
Excessive alcohol consumption	History of alcohol consumption >20 g/day—females History of alcohol consumption >30 g/day—males
Drugs history of drug exposure	Tamoxifen, valproate, oestrogens, corticosteroids, tetracycline, amiodarone, perhexiline maleate, methotrexate, chloroquine, L-asparaginase
Exposure to toxics	History of occupational exposure to hepatotoxins
Malnutrition; Kwashiorkor; Total parenteral nutrition; rapid weight loss; jejuno-ileal bypass, extensive resection of small bowel	Clinical history
Lipodistrophy, hypobetalipoproteinemia	Clinical history; laboratory evaluation
Celiac disease	Anti-tissue transglutaminase antibodies positive

If large samples of the population are to be investigated in relation to the presence of NAFLD, serum tests are preferable, due to cost and accessibility issues. There are several scores that have been validated, such as the fatty liver index (FLI), the SteatoTest and the NAFLD liver fat score. These scores have been shown to predict the presence of steatosis, but not the severity [21].

Frequently, the suspicion of NAFLD arises due to abnormal aminotransferases or the finding of steatosis in an US usually done for another reason. At this point, there is need to exclude other causes of fatty liver, the most important being excessive alcohol consumption, with a careful history of alcohol consumption. It is increasingly frequent the coexistence of excessive alcohol consumption with metabolic factors, contributing to steatosis; however, an alcohol consumption of more that 20 g in women and 30 g in men, by definition, excludes NAFLD as a diagnosis [7].

Several other states as well as steatogenic drugs have been associated with the presence of steatosis, and need to be excluded (Table 12.1).

12.3 Diagnostic Algorithm

After establishing the diagnosis of NAFLD, it is necessary to evaluate the severity of the disease, in order to decide who are the patients that need to be referred to a specialist consultation.

The dichotomy between patients with NAFL, i.e., simple steatosis on histology and NASH, those with the necro-inflammatory histologic picture NAFLD spectrum, no longer seems so significant. In fact, it is increasingly recognized through

long-term follow-up studies that patients with simple steatosis can also progress to advanced liver disease, and that it is the degree of fibrosis the major predictor of progression and mortality [19, 20, 22]. Consequently, it became more relevant to stage liver fibrosis than to identify the presence of NASH [7, 8, 23].

Although the gold standard for the diagnosis and staging of NAFLD is still liver biopsy (LB) [24], there is no role for its use in primary practice. The major point is the identification of those patients that have more severe fibrosis and need referral, leaving the decision of doing liver biopsy for the specialist.

12.3.1 Staging for Liver Fibrosis

There are several methods that can allow us to predict who are the patients with advanced fibrosis (Table 12.2). These methods should be used in a stepwise approach, by first ruling out advanced fibrosis, benefiting from their high negative predictive value for advanced fibrosis.

Evaluation should start the simplest noninvasive methods, such as validated scores that can be easily calculated from regular blood tests and anthropometric and clinical data, direct fibrosis blood tests (commercial), and test for evaluation of liver fibrosis. Liver biopsy should be reserved for patients with suspected advanced fibrosis or for those patients where there is no concordance among results.

12.3.2 Scores: NAFLD Fibrosis Score and Fibrosis Score 4

Both scores perform quite well in excluding severe fibrosis and have been well validated. General practitioners (GP) can use them in their everyday practice since the

Table 12.2 Methods for staging liver fibrosis in NAFLD patients

Method		Advanced fibrosis
Scores (biochemistry ±anthropometry)	NAFLD fibrosis score Fibrosis-4 score (FIB4)	>0.676 [25] >2.676 [26]
Blood test (commercial)	Enhanced liver fibrosis (ELF)	≥10.51 [27]
Measurement of liver stiffness	Transient elastography: FibroScan with M or XL probes Acoustic radiation force impulse elastography (ARFI) Magnetic resonance elastography (MRE)	> 8.7 Kpa [28] >1.4 m/s [29] >3.64 [30]

NAFLD fibrosis score: $-1.675 + 0.037 \times \text{age} + 0.094 \times \text{BMI} + 1.13 \times \text{IFG or diabetes (yes = 1, no = 0)} + 0.99 \times \text{AST/ALT ratio} - 0.013 \times \text{platelet count} - 0.66 \times \text{serum albumin}$

FIB-4: $(\text{age} \times \text{AST}) (\text{platelet count} \times \sqrt{\text{ALT}})$

formulas are based on simple and routine biochemical tests or anthropometric measurements that can be incorporated in the database system or downloaded on line.

NAFLD fibrosis score (NAFLD FS) is probably the most widely used score, with a very good capacity for ruling out advanced fibrosis [25]; however, the performance is poor for the diagnosis of advanced fibrosis, furthermore classifying about 20–58% in the indeterminate area [31].

In what concerns FIB4 index, a value of <1.3 showed a 90% negative predictive value, while a value of FIB≥2.67 had an 80% positive predictive value for significant fibrosis [26].

The use of commercial tests such as the ELF test that combine three direct fibrosis tests (i.e., tissue inhibitor of metalloproteinase 1, procollagen III N-terminal peptide, and hyaluronic acid) has been shown a good performance and considerable diagnostic value for the prediction of histological fibrosis stage [32]. However it carries economic costs and is less accessible to be used by the GP.

Just by using the first two scores, NAFLD FS and FIB4, GP could rule a significant number of NAFLD patients who have scores below the threshold of significant fibrosis. These patients, all the same should undergo counseling for lifestyle interventions concerning dietary measures and physical activity advise. Also, it is very easy to repeat these scores in a 2 or 3 years time, as proposed by EASL guidelines.

Another possibility, if there is availability, is to use methods to evaluate liver stiffness.

12.3.3 Elastography Measurements

12.3.3.1 Transient Elastography (TE), Using FibroScan with M or XL Probes

The use of TE is quite easy and reproducible. It is not a difficult procedure to learn, and can be performed after minimal training (about 100 examinations), by a medical doctor, a nurse or a technician [33]. It can be performed as a point-of-care test, simultaneously estimating the degree of hepatic steatosis and fibrosis, and has shown higher accuracy in diagnosing advanced fibrosis than the above-mentioned fibrosis prediction scores [34–36]. The major problem with the application of TE is that although it has an excellent sensitivity and a high negative predictive value (NPV) [28, 37–41], thus allowing the exclusion of advanced fibrosis, it has a low positive predictive value (PPV), leaving us with a group of patients that need further confirmation of advanced fibrosis. That confirmation can be done by liver biopsy, or another non-invasive test [42]. Recently it was

demonstrated that by repeated measurement of TE in cases of high liver stiffness measurement (LSM), about one-third of cases will not be confirmed as high, increasing the PPV from 45% to 61% and reducing the number of liver biopsies needed [43].

12.3.3.2 Acoustic Radiation Force Impulse Elastography (ARFI)

ARFI is an ultrasound-based technique that is quite cheap, and can be used during the ultrasound procedure. It has been shown accuracy for the diagnosis of fibrosis although it is a technique with some degree of operator dependency [44, 45]. In a head-to-head comparison with magnetic resonance elastography (MRE), it was less accurate to diagnose fibrosis in obese NAFLD patients [46].

12.3.3.3 Magnetic Resonance Elastography (MRE)

Regarding MRE, it has been shown that using a stiffness cutoff of 3.63 Kpa, an AUROC of 0.924 for diagnosing advanced fibrosis is obtained [47]. If, in addition, a three dimensional (3D) MRE is used with a stiffness cutoff of 2.43, then an AUROC of 0.962 for diagnosing advanced fibrosis is obtained [48]. In fact, this technique has the higher accuracy for fibrosis staging in NAFLD [30, 34], but it is not a practical tool for primary care practice, due to accessibility and costs. It should be reserved for referral centers.

There is also the possibility of combining the scores with elastography, as suggested by Cahn et al., using a novel two-step approach [49].

12.4 Summary

In the primary care setting, GPs should have a great level of suspicion for NAFLD, particularly in high-risk groups. As shown in Fig. 12.1, when facing the evidence of steatosis, usually through ultrasound, the next step is ruling out causes such as excessive alcohol consumption or other steatogenic situations or medications. To assess the risk of progressive disease, probability of advanced fibrosis degree can be calculated by the use of combined scores such as NAFLD FS or FIB-4. If the scores are negative, they can be repeated in 2 or 3 years. If the scores are indeterminate or positive, the patient can either be immediately refereed to a specialist consultation, or undergo an elastography method, such as Fibroscan or ARFI, if there is availability.

If the patients with elevated risk of fibrosis are referred precociously, this will be able to decrease the morbidity and mortality of NAFLD-related liver disease.

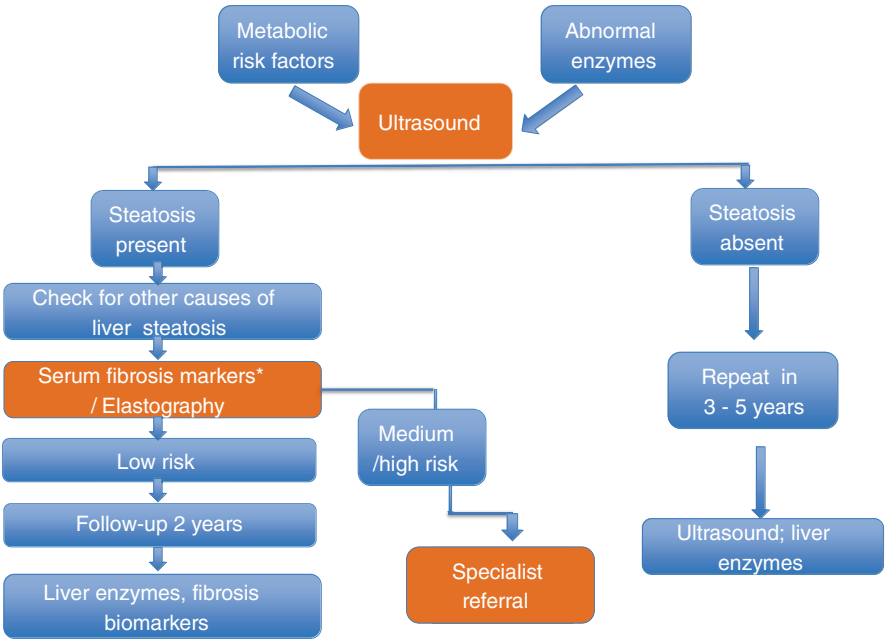

Fig. 12.1 Algorithm for decision in primary care. *Serum fibrosis markers: NAFLD Fibrosis Score, FIB-4, commercial tests (FibroTest, FibroMeter, ELF). (Adapted from NAFLD EASL guidelines [7])

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