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Non-alcoholic fatty liver disease: a multidisciplinary clinical practice approach—the institutional adaptation to existing Clinical Practice Guidelines

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is among the most frequently encountered chronic liver diseases in everyday clinical practice. It is considered the hepatic manifestation of metabolic syndrome. Today, liver biopsy is still the gold standard for NAFLD confirmation and assessing NAFLD's possible progression to non-alcoholic steatohepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma. Because of the high prevalence of NAFLD and potential associated risks of invasive diagnostic procedures, it is of great interest to recruit the patients for liver biopsy. However, as the presence of liver fibrosis determines the further clinical course, liver biopsy is expectedly reserved for those with increased fibrosis risk. The quality of liver biopsy recruitment and patient monitoring could be significantly improved by using non-invasive tools to assess liver fibrosis presence and interactive collaboration between general practitioners, gastroenterologists, and endocrinologists. As a result, the quality of liver biopsy recruitment and patients monitoring could be significantly improved. Here, we proposed clinical practice guidelines that could be implemented for everyday clinical practice in NAFLD patients.

Keywords: Diagnostics of NAFLD, Fatty liver index, Fibrosis score-4, Management of NAFLD, Non-alcoholic fatty liver disease

Introduction

Non-alcoholic fatty liver disease (NAFLD) is presented by excessive lipid accumulation in the liver. It is defined as the presence of steatosis in >5% hepatocytes in histology specimen or >5.6% liver lipid content measured by proton spectroscopy magnetic resonance imaging (^{1}H-MRS).[1] To confirm the diagnosis of NAFLD, the exclusion of other liver lipid deposition causes is necessary, such as alcoholic drinks consumption, other chronic liver diseases (viral, autoimmune, metabolic), as well as the use of different steatogenic drugs (amiodarone, corticosteroids, numerous antimicrobial, and cytotoxic agents).[1–3]

Fatty liver is represented by NAFLD and non-alcoholic steatohepatitis (NASH). As the link between NAFLD and metabolic syndrome (MetS) components is strong, NAFLD is recognized as a hepatic manifestation of MetS.[4] Hence, liver steatosis is more frequently occurred in obese patients (about 45%) and ones who suffered from type 2 diabetes mellitus (t2DM) (about 70%).[5] On the other hand, the risk of t2DM in NAFLD patients is significantly increased.[6]

NAFLD is considered the most frequent chronic liver disease, with an overall prevalence of about 25%.[3,7,8] Considering the general population, it is estimated that 34%–36% and 12% of patients suffered from NAFLD and NASH.[5,9,10] In Western countries, the estimated prevalence of NAFLD in adults is 17%–46%.[5,9,11] Taking all into account, it seems that >1 billion people suffered from NAFLD, and >400 million suffered from NASH worldwide.[12] Regarding the complications of NASH, liver cirrhosis caused by NASH is the leading cause of hepatocellular carcinoma (HCC) and the second leading indication for liver transplantation in the United States.[13,14] Despite its high prevalence, it is noteworthy that most patients are not diagnosed with NAFLD.[2,15] It is now clear that numerous cases of cryptogenous liver cirrhosis in the past are, in fact, NASH-induced. Additionally, HCC can be detected in NASH subjects with no liver cirrhosis.[16]

NAFLD is a slowly progressive disease in adults, as well as in children. It is evidenced that about 80% of NAFLD will remain in the stable form of the disease, but about 20% will develop NASH.[17] The accelerated development of liver fibrosis can occur in every fifth NAFLD patient.[18]

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The exact pathogenesis of NAFLD is not fully elucidated. Multiple hit and organ theory is now widely accepted.[19] The first step is decreased lipolysis inhibition in visceral fat contributed by abdominal obesity and/or insulin resistance. That leads to the increased influx of free fatty acids (FFAs) in the liver and contributes to liver steatosis.[20] An increase in de novo lipogenesis and decreased lipid efflux from the liver also contributes to liver steatosis of NAFLD.[21] Accumulation of triacylglycerol deranges insulin-dependent liver energy metabolism, disturbed hepatic gluconeogenesis, and VLDL lipoprotein synthesis. The second step in NAFLD pathogenesis is the development of inflammation, oxidative stress, and fibrosis. The transfer from NAFLD into NASH is registered in 1/3 NAFLD patients.[22–26]

As a progressive form of NAFLD, the histology hallmark of NASH is the presence of inflammation, with or without liver fibrosis.[27,28] About the third of patients with NAFLD progress into liver fibrosis, another third remain in stable disease, and the left third restore.[29] The progression rate is associated with an almost 350% increase in cardiovascular disease morbidity.[24] Furthermore, hepatic disease progression is frequently related to the worsening of metabolic parameters, such as HOMA IR, a surrogate marker of insulin resistance.[30,31]

The risk of fibrosis to some extent is genetically determined. Determined genetic determinants, such as single nucleotide determinants (SNPs), influence the increase in fibrogenesis incidence and progression.[32,33] Some polymorphisms (change of Ile with Met on 148 codon of PNPLA-3 or Glutamate change with Lysine on 167 codon of TM6SF2) are associated with a higher risk of liver steatosis, NASH, cirrhosis, and HCC.[33] Some clinical and non-invasive markers could be beneficial in predicting liver fibrosis risks, such as an increase in alanine aminotransferase (ALT) and aspartate aminotransferase (AST), increase in body weight (>5 kg), low platelet count, increase in non-invasive liver steatosis, and fibrosis scores, the presence of t2DM.[34,35] The end-stage of hepatocytes' functional disintegration in their apoptosis. The apoptosis rate in NAFLD/NASH patients is significantly increased. Serum ferritin levels could biochemically predict the progression of NAFLD toward NASH.[36,37]

NAFLD

Previously NAFLD has been defined as the liver fat accumulation, based on radiological or histological analyses, in the lack of other liver disease or causes of steatosis.[38] However, considering that NAFLD is a spectrum ranging from simple steatosis (NAFL) to NASH and cirrhosis, where NAFL is characterized by steatosis in at least 5% of hepatocytes, it has been proposed to rename NAFLD.[39–42] The more appropriate definition of this disease would be metabolic (dysfunction)-associated fatty liver disease (MAFLD), since NAFLD is strongly associated with obesity and diabetes.[41,42] Although this initiative has been generally well accepted,[43–45] consideration to change NAFLD's name to MAFLD is still ongoing.[40,46,47]

The pathogenesis of NAFLD is a complex, incompletely explored process, initially described as a *two-hit* hypothesis.[48] In this theory of NAFLD origin, the *first hit* refers to liver fat accumulation and insulin resistance. In contrast, the *second hit* implies increased inflammatory cytokines, adipokines, mitochondrial dysfunction, and oxidative stress, promoting further disease progression to hepatic steatosis and ultimately cirrhosis.[49] Eventually, this theory was replaced with a *multiple-hit* hypothesis, a more comprehensive theory for NAFLD pathogenesis since it involved metabolic dysfunction caused by genetic and environmental factors and interaction between the liver, adipose tissue, pancreas, and gut.[49–51] Furthermore, the emergence of the *multiple-hit* hypothesis and development of data analysis tools such as GWAS that focused on gene variants predisposed to altered lipid and sugar metabolism is a step forward in NAFLD diagnostics and identification of subjects at risk for NAFLD.[51]

Diagnostics

Screening

Patients with insulin resistance (IR) and/or MetS risk factors should be screened for NAFLD presence.[1] On the other hand, patients with liver steatosis should be screened for the components of MetS and examined for other secondary causes of liver steatosis and abuse of alcoholic drinks.[1] Despite the very high prevalence of NAFLD, most Guidelines do not recommend routine screening on NAFLD/NASH.[1]

The screening on fibrosis presence is obliged for the patients with already diagnosed NAFLD/NASH.[32] For NAFLD detection and stratification, serum transaminases and abdominal ultrasound performance measurement seem insufficiently sensitive. In most patients with NAFLD, liver function tests were normal in 79% of subjects, including liver fibrosis in advanced stages.[52] Additionally, moderately high liver lipids content is necessary to detect and describe NAFLD on abdominal ultrasound (AUS) scanning. Those, as mentioned earlier, are the possible reasons for withdrawal of systemic screening for NAFLD/NASH.[32,53]

Management of NAFLD

Diagnosis of NAFLD requires the elimination of other secondary causes of liver steatosis such are alcoholic and metabolic liver diseases, drug-induced or viral hepatitis, inborn metabolic errors, hypothyroidism, hypopituitarism, starvation, parenteral nutrition, and others, including and everyday consumption of alcoholic drinks (>20 g and 30 g of total daily alcohol intake in men and women, respectively).[54] NAFLD could be detected by AUS and magnetic resonance imaging.[55]

For liver steatosis detection, abdominal ultrasound possesses expectedly lower sensitivity. It is insufficiently sensitive when the liver lipids contents are <20% or in the cases of obese patients with body mass index >40 kg/m^2.[56,57] Also, non-invasive scores, such as fatty liver index (FLI), could point out just presence, but not the severity of liver steatosis.[1,58] Such a non-invasive tool is helpful in specific circumstances (i.e., AUS or staff are not available).[58] The gold standard for non-invasive assessment of liver lipids content is ^{1}H-MRS.[1,59] The most precise tool is histology analysis of liver specimens obtained by liver biopsy.[60,61]

As the NAFLD is a hepatic manifestation of MetS, it is expected to be associated with an increased incidence of cardiovascular diseases (CVDs).[4] CVDs significantly contribute to mortality risk more common than an end-stage chronic liver disease in patients with NAFLD.[62] Such CV risk becomes more stressed with diabetes development.[63] Hence, the screening of CVDs is strongly advised in patients with NAFLD.[64] The linking between NAFLD and subclinical or clinical CVDs include endothelial dysfunction, atherogenic dyslipidemia, procoagulopathy, systemic inflammation, altered GUT microbiota, and associated genetics and epigenetics alterations.[65,66] Clinical presentation of NAFLD-associated CVDs is diverse, including hypertension, cardiac dysrhythmias, and spectrum of atherosclerotic CVDs (ASCVDs).[67] Besides managing MetS components, thorough assessment and stratification of CV risk factors are mandatory in NAFLD patients.[68,69]

Diagnostics of NASH

To confirm NASH, it is necessary to analyze liver biopsy specimen histologically.[1,70,71] The significance of NASH histological confirmation is presumably prognostic: predicting progression rate into fibrosis, cirrhosis, and assessing the risk of HCC. Despite some inter-and intraobservational differences in liver histology findings, it is still the most reliable method regarding NASH confirmation and clinical course prediction.[1,70,72,73]

Guidelines

Guidelines suggest AUS as the first method in NAFLD detection.[1] Although the magnetic resonance imaging tools are more sensitive and accurate than AUS in detecting and quantifying liver steatosis, they are less available.[74] After liver steatosis detection, the exclusion of secondary causes of liver steatosis must be performed (i.e., data from past medical and family history and laboratory findings). Simultaneously, a thorough examination of the components of MetS is performed.[1,75]

Non-invasive (surrogate) markers of liver fibrosis (e,g., Fib-4) it is recommended to be calculated at the level of primary care for every patient individually in order to exclude the presence of severe liver fibrosis (stage F≥3).[64,76] If the non-invasive liver fibrosis score points out to the moderate or high risk of severe fibrosis, then the patient is referred for further diagnostics consisting either of biochemical test performance that measure the components for extracellular matrix (for example, enhanced liver fibrosis test or Fibrometer) or transitional elastography (TE) of the liver. Transitional elastography of the liver is the best validated and most exploited liver stiffness measurement (LSM) tool. In the cases of LSM <8 kPa, significant fibrosis is excluded. If the values of LSM are >9.5 (10) kPa and >15 kPa, they point out severe liver fibrosis or compensated chronic liver disease and liver cirrhosis, respectively.[77,78] In the case, the second level test shows on advanced chronic liver diseases; the patient must be referred to a gastroenterologist for further follow-up regarding detection portal hypertension markers and other complications of progressive chronic liver disease (esophageal varices and HCC).[79]

If non-invasive liver fibrosis scores should not exclude severe liver fibrosis, the patient is referred to a gastroenterologist concerning TE. If liver TE demonstrates significant liver fibrosis, it is obliged to obtain a liver tissue specimen by liver biopsy. The risk factors for the presence and aggravation of liver fibrosis are age (>50 years), t2DM, and genetic predisposition.[32,80]

Although liver histology is the most accurate and reliable diagnostic tool for assessing liver fibrosis presence and severity,[23,71] some simple, non-invasive liver fibrosis scores could help detect significant liver fibrosis presence.[72] The use of TE significantly contributes to the better accuracy of non-invasive scores. Transitional elastography of the liver was shown as more sensitive in the detection of liver cirrhosis (stage F4 of liver fibrosis) than in the cases of advanced liver fibrosis (stage F3).[81] Combining non-invasive scores and TE increases diagnostic accuracy in detecting significant liver fibrosis contributing to lowering liver biopsy performances.[1] Simultaneously, the detection or high suspicion on liver fibrosis progression or cirrhosis presence using non-invasive scores and TE should point out to clinicians on obliged liver biopsy performance.[1]

Even though several international guidelines for NAFLD assessment were published and supported by reputable scientific societies with experts in hepatology, there are still numerous inconsistent attitudes. Some of them are the definition of NAFLD, recommendations for clinical practice, screening strategies in high-risk subjects, favorable non-invasive tests, and biomarkers for NAFLD diagnosis, selecting patients to liver biopsy and therapy approach.[82,83] However, these variances rather are caused by population specificity, such as genetic predisposition to NAFLD, lifestyle, primary health care, than the inability to find consensus.[82,83] Among other high-risk subjects, those with diabetes or obesity should be systematically screened for NAFLD since evidence indicates higher NASH frequency and advanced fibrosis stages in patients with type 2 diabetes.[84,85] Furthermore, evidence indicates that screening for NASH in subjects with diabetes is not cost-effective.[86] Liver biochemical parameters as a screening tool for NAFLD are not sufficiently sensitive given the high number of false false-negative results. In contrast, a potentially sensitive method such as liver ultrasound or TE still is not proven.[86,87] The progression and development of new technologies in NAFLD diagnostics and therapy will contribute to finding a unified position for NAFLD management.[87]

The authors strongly encourage the use of existing Clinical Practice Guidelines but additionally favor the use of local or institutional guidelines according to acquired experience in everyday clinical practice.

Non-invasive liver steatosis and fibrosis diagnostic tools

The existing imaging tools in liver steatosis diagnostics (AUS, abdominal computed tomography, magnetic resonance imaging, and ^{1}H-MRS) show 80%–94% sensitivity.[88,89] No one of the tools mentioned above can detect fibrosis[90] or make a difference between NAFLD and NASH.[91]

The ideal non-invasive diagnostic tool for assessing liver fibrosis's presence and severity should be sensitive enough, specific, available, and applicable in various liver diseases. Concerning NAFLD, such a tool should make a difference between NAFLD and NASH. However, no one of the currently used non-invasive tools fulfills mentioned criteria.[92] Non-invasive diagnostic tools could be repeated during the time. In the cases of confusing results, one can use ≥2 scores in addition to non-invasive imaging tools.[93] The entire cluster of non-invasive tools is intended to detect significant liver fibrosis presence (stage ≥F3), but not for the lower fibrosis stages independently of the etiology of chronic liver disease, including hepatitis C virus (HCV)/human immunodeficiency virus (HIV) co-infected.[93–95]

AUS is the most commonly used method for diagnosing NAFLD due to its most comprehensive availability, simplicity, and low cost of the examination. In addition, it is easily applicable to all patients. European guidelines for treating NAFLD recommend using ultrasonography as the first-line diagnosis in adults at risk of NAFLD.[63] Ultrasound assessment of hepatic steatosis is limited due to its low sensitivity and safety,[96] especially in the lower degrees of steatosis, with significant inter-observer variability[97,98] and is often not feasible in patients with high BMI.[99] Despite being based on subjective assessment, AUS has good sensitivity and specificity in detecting moderate and severe degrees of steatosis (84.8% and 93.6%, respectively). In comparison, the overall sensitivity and specificity of the method are lower due to more considerable differences in assessment of mild steatosis (65% and 81%, respectively).[89] AUS usually detects steatosis only in more than 20% of the fatty content in the liver. Five to twenty percent of fat in the liver often cannot be detected by AUS.[100] Overcoming the problems with subjective assessment and inaccuracy in the gradation of steatosis in conventional AUS are made by significant progress in the development of quantitative AUS techniques such are: controlled attenuation parameter (CAP), attenuation (AC), and backscatter coefficients (BSC); computerized calculation of hepatorenal index (HRI), acoustic structure quantification (ASQ), Nakagami imaging, speed of sound (SoS), and other.[100,101]

Among the most frequently used non-invasive imaging tools for detecting liver fibrosis presence and severity is TE.[102] Liver transitional elastography and its modifications (i.e., magnetic elastography) were shown as exceptional in assessing liver elasticity that inversely correlated with liver fibrosis.[103,104] The use of liver

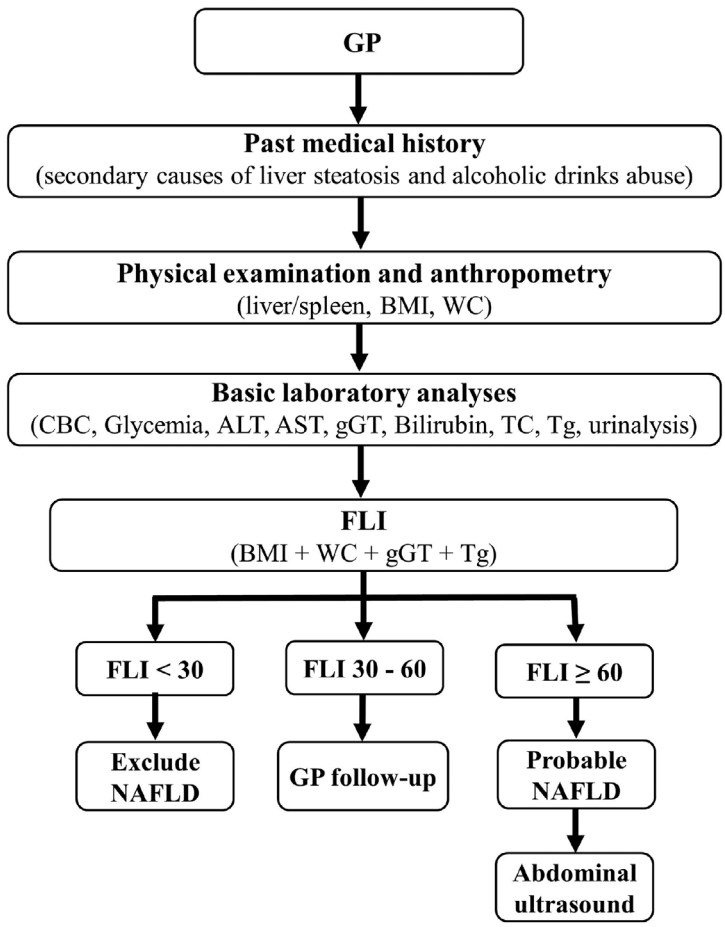

Figure 1. Schematic presentation of a practical guide for managing the patients with NAFLD with a focus on the role of GP. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CBC, complete blood count; FLI, fatty liver index; gGT, gamma-glutamyl transferase; GP, general practitioner; NAFLD, non-alcoholic fatty liver disease; TC, total cholesterol; Tg, triglycerides; WC, waist circumference.

fibrosis biomarker/s could help clinicians assess chronic liver disease progression or the quality of response to applied non-pharmacological, pharmacological, or innovative (antifibrotic) treatment.[93]

Non-invasive liver steatosis and fibrosis scores are composed of clinical and biochemical parameters that are frequently used in everyday clinical practice.[92,105] Because of simplicity in their use, they could be used on GP and specialty outpatients'. Current guidelines suggest using non-invasive liver steatosis scores in NAFLD/NASH patients to recruit patients for AUS and identify or exclude advanced stages of liver fibrosis.[1,54,106,107]

Biomarkers in the diagnosis of NAFLD/NASH. In clinical practice, especially in general practitioners (GPs), the use of widely available serum biomarkers to assess the risk of NAFLD/NASH is crucial. Most non-invasive markers in the widest use date back more than a decade, but many new tests await validation. One of the most commonly used scores is the NAFLD Liver Fat Score (NLFS). It can indicate the fat content in the liver tissue. It is based on assessing parameters including the presence of metabolic syndrome, type 2 diabetes, fasting serum insulin, fasting serum AST/ALT ratio (AAR). The sensitivity of the test in the prediction of NAFLD depends on the limit value taken. For test values > -0.640, the sensitivity in NAFLD prediction is 86%, specificity 71%.[20] The need to determine fasting insulin levels, which is not a routine test in daily clinical practice, reduces the broad applicability of the test.

The Hepatic Steatosis Index (HIS), which evaluates the AST/ALT ratio, BMI, diabetes, and sex, has a specificity of 69% and a sensitivity of 66% in the prediction of NAFLD, but the results were validated only with the US and not with liver biopsy findings.[108] FLI was also compared primarily with the US and showed promising results in detecting fat in the liver. The index includes serum biomarkers triglycerides, gamma-glutamyltransferase, BMI, and waist circumference.[109] In addition to these widely available serum biomarkers that can be routinely performed in any laboratory, commercial panels are used to assess liver steatosis, which, based on the calculation of several serum biomarkers, calculates scores to assess the degree of liver steatosis. Some of them are SteatoTest (Biopredictive, France) which combines six components of Fibro Test Acti Test (Biopredictive) and the level of total serum bilirubin, ggT, alpha macroglobulin, haptoglobin, ALT, and apolipoprotein A, plus BMI, the level of serum total cholesterol, triglycerides and glucose, age- and sex-adjusted.[110] Because tests are commercial and not widely available, this limits their use in everyday clinical practice. All these serum biomarkers are mainly surrogate markers of liver fat and cannot reliably assess the degree of steatosis, where different imaging techniques give significantly better results. In the diagnosis of NASH, that is, distinguishing NASH from steatosis, so far, no serum biomarker has shown high sensitivity and specificity. The use of cytokeratin 18 fragments that accumulate during cell death (M65 fragment) and apoptosis (M3) show some degree of sensitivity (66%) and specificity (82%) in the diagnosis of NASH.[111] Other individual biomarkers have also been evaluated in a similar context, such as the inflammatory biomarkers TNF and IL 8 and the hormones

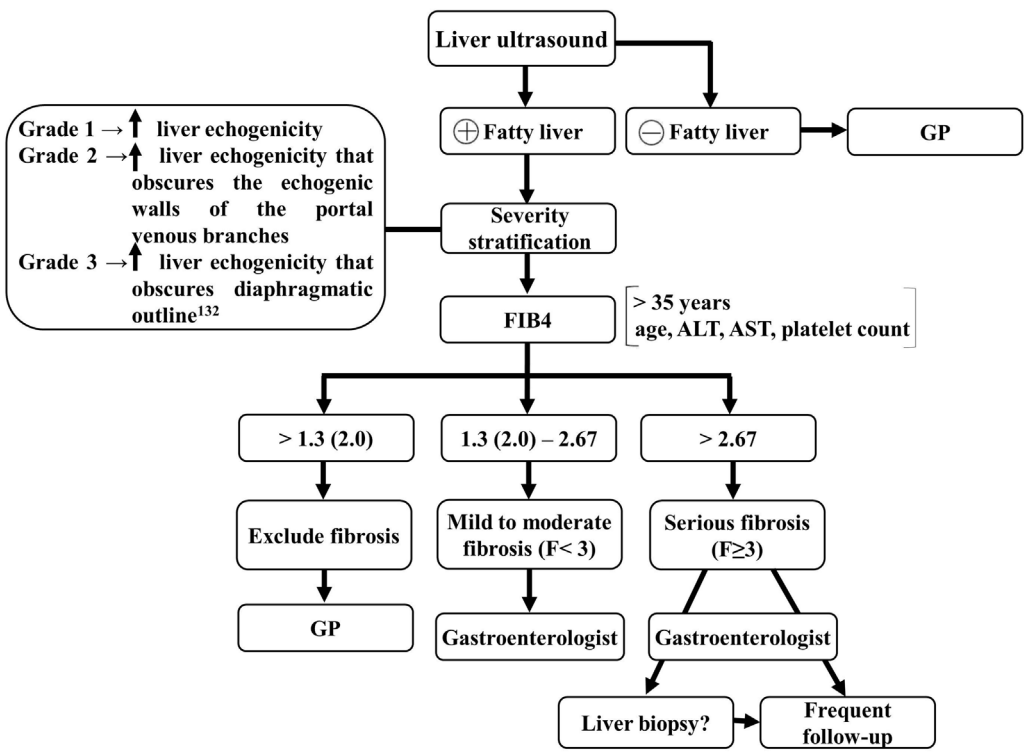

Figure 2. Schematic presentation of a practical guide for managing the patients with NAFLD focused on liver ultrasound approach. GP, general practitioner; FIB4, fibrosis score-4; ↑ indicate an increase. According to the study Singh et al.[127]

adiponectin, for example. Some other tests combine multiple serological biomarkers. For example, the NASH test combines 13 different biomarkers and clinical variables (age, sex, body weight) and serum levels of triglycerides, cholesterol, α-macroglobulin, apolipoprotein A1, haptoglobin, ggT, ALT AST, and total bilirubin), and can assess the presence or absence of NASH with 0.79 AUROC.[112] However, this test also uses serum biomarkers not used in routine clinical practice, affecting limited use in outpatient settings. Of course, the evaluation of new serum biomarkers is still recommended to make the NAFLD/NASH assessment as practical and accessible as possible, but many are available in clinical studies and are awaiting confirmation in clinical work.

Fatty liver index. The fatty liver index (FLI) score is a simple diagnostic tool that could help select clinician patients for AUS in those suspicious of liver steatosis. FLI score ≥60 points out the necessity of non-pharmacological and pharmacological measures intensification in the management of NAFLD patients. Additionally, clinicians should be warranted to refer the patient to a non-invasive liver fibrosis score calculation.[113–116] FLI score values range from 0 to 100. FLI score ≥60 showed good sensitivity and specificity (87.3% and 80.3%, respectively) to detect NAFLD presence by AUS. On the contrary, FLI <30 excludes NAFLD's possibility.[113,114,117,118] The diagnostic accuracy of FLI regarding liver steatosis detection is 84% (95% CI 81%–87%).[113] FLI could predict t2DM and atherosclerotic cardiovascular disease, as well as a 15-year mortality rate associated with chronic liver disease.[119,120] Therefore, the FLI score is both a diagnostic and prognostic marker.[58]

Fibrosis score-4 (Fib-4). Among the most frequently used non-invasive scores for liver fibrosis assessment is Fib-4.[95,109] Sterling et al.[95] constructed a Fib-4 score with reliable predictivity regarding liver fibrosis detection and differentiation from mild to severe fibrosis and cirrhosis. Initially, it was intended as the non-invasive score for chronic liver disease severity stratification in HCV/HIV co-infected patients.[121] Concerning its simplicity; it can be used even on GP level.[92,95] Additionally, Fib-4 was shown as a very reliable score for NASH detection (AUROC 0.86–0.90).[122]

Fib-4 demonstrates important roles in severity stratification of NAFLD/NASH patients regarding liver fibrosis presence. Also, it could be an essential tool for the liver biopsy selection of patients with a higher risk of serious complications associated with chronic liver disease.[59] Because the patient's age significantly influences Fib-4 interpretation, alternative methods for detecting and severity stratification of liver fibrosis are recommended for patients <35.[94,123]

Fib-4 values <1.3 (<2.0) exclude liver fibrosis, but values >2.67 show on advanced stages of liver fibrosis (stage F ≥ 3). The correction for lower reference values for Fib-4 in the patients ≥65 years improved specificity (77%), AUROC 0.75–0.88, with no influence on sensitivity.[124] Besides its role in selecting NAFLD/NASH patients for liver biopsy, it could be used as a prognostic marker to predict t2DM and HCC presence.[64,92,125,126]

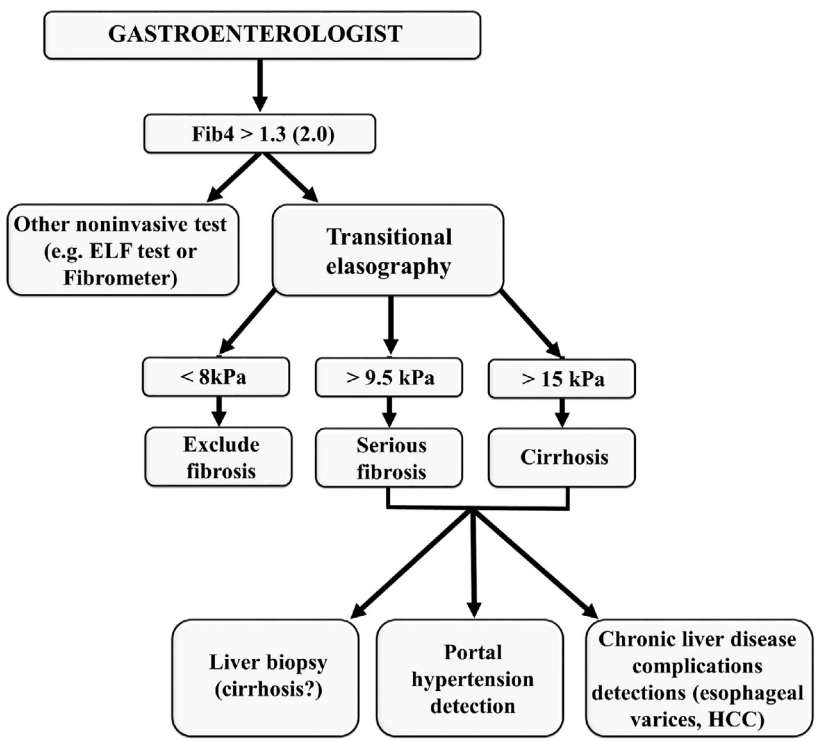

Figure 3. Schematic presentation of a practical guide for managing the patients with NAFLD focused on a gastroenterologist's role. ELF, enhanced liver fibrosis test; FIB4, fibrosis score-4.

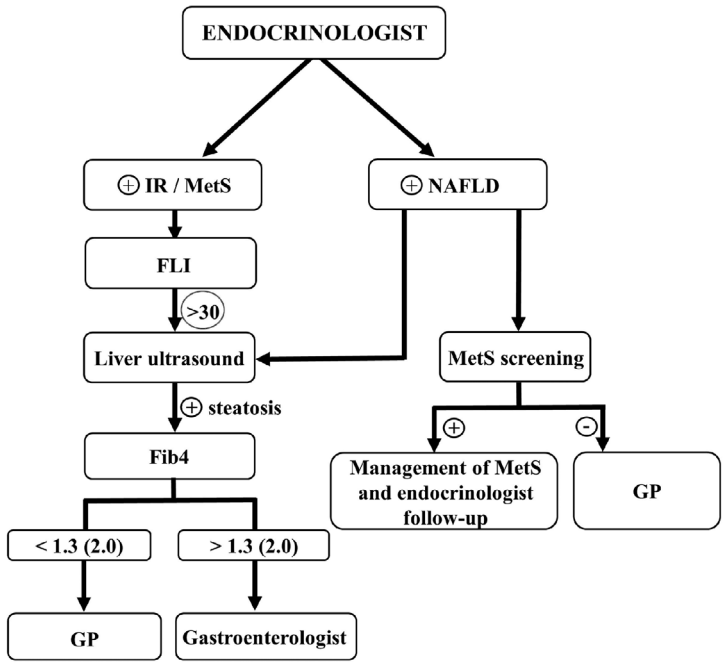

Figure 4. Schematic presentation of a practical guide for managing the patients with NAFLD focused on an endocrinologist's role. CRP, C-reactive protein; FIB4, fibrosis score-4; FLI, fatty liver index; GP, general practitioner; HbA1C, glycosylated haemoglobin; HDL, high-density lipoprotein particles; IR, insulin resistance; LDL, low-density lipoprotein particles; Lp(a), lipoprotein (a); MetS, metabolic syndrome; NAFLD, non-alcoholic fatty liver disease; oGTT, oral glucose tolerance test; oxLDL, oxidized low-density lipoprotein particles; TSH, thyroid-stimulating hormone.

Figures 1–4 present the practical guide for applying non-invasive tools to manage patients with NAFLD/NASH. By intensive collaboration between GP, endocrinologist, and gastroenterologist, all NAFLD/NASH disease aspects are covered: preventive, hepatologic, and metabolic.

Conclusion

The excessive growth of NAFLD patients worldwide clearly shows the necessity for improved interaction and collaboration between GP, gastroenterologists, and endocrinologists. This collaboration aims to recruit patients who are at high risk for progressive liver disease. Individual approach to every NAFLD patient, and local, more flexible, and organized referral pathways provide more appropriate management of patients. The health care system's burden should be more uniformly balanced by these interactive and well-developed local referral pathways. Additionally, to every individual patient belonging, health care service could be provided.

Conflict of interest statement

The authors declare no conflicts of interest.

Author contributions

Gluvic Z designed and wrote the paper, Tomasevic R, Bojovic K and Obradovic M, wrote the paper Isenovic ER wrote, designed, supervised, and critically revised the paper.

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Ethical approval of studies and informed consent

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