REVIEW ARTICLE

General Overview About the Current Management of Nonalcoholic Fatty Liver Disease

Javier Ampuero[1,2,3,4]

Abstract

Nonalcoholic fatty liver disease includes a wide spectrum of manifestations from simple steatosis to nonalcoholic steatohepatitis, fibrosis, and eventually cirrhosis or even hepatocellular carcinoma. This disorder is also associated with an increased cardiovascular risk, renal involvement, oncologic processes, metabolic disturbances, and an increased risk of all-cause mortality or hepatic mortality. For this reason, nonalcoholic fatty liver disease should be considered a disorder with high morbidity and mortality that must be diagnosed appropriately as soon as possible to establish adequate treatment. Noninvasive methods based on biochemical parameters should be used as a first step in the evaluation of any patient in whom this disease is suspected. However, serum/blood levels of liver enzymes are not a good indicator of liver damage and noninvasive methods, including biochemical tests and imaging, have suboptimal accuracy or are patented prototypes that show limitations in clinical practice. There are currently no drugs specifically approved for the treatment of these liver disorders, thus the most relevant intervention for nonalcoholic fatty liver disease is lifestyle modification.

Key Points

Nonalcoholic fatty liver disease is a disorder with high morbidity and mortality that includes a wide spectrum of hepatic and extrahepatic manifestations that should be properly diagnosed to establish an appropriate treatment.

Noninvasive methods based on biochemical parameters should be used as a first step in the evaluation of any patient in whom this disease is suspected. However, serum/blood levels of liver enzymes are not a good indicator of liver damage and biochemical tests and imaging have suboptimal accuracy.

There are currently no drugs specifically approved for the treatment of these liver disorders, thus the most relevant intervention for nonalcoholic fatty liver disease is lifestyle modification.

✉ Javier Ampuero
  jampuero-ibis@us.es

1   Hospital Universitario Virgen del Rocío, Calle Alonso
    Carrillo, Sevilla, Spain

2   Instituto de Biomedicina de Sevilla, Sevilla, Spain

3   Universidad de Sevilla, Sevilla, Spain

4   CIBERehd, Madrid, Spain

1 Introduction

Nonalcoholic fatty liver disease (NAFLD) is defined as hepatic steatosis in more than 5% of the liver in the absence of relevant alcohol intake (more than 30 g of alcohol per day in men and more than 20 g of alcohol per day in women) [1]. However, because of the possibility of steatosis despite moderate alcohol consumption and to better reflect the pathogenesis of the disease, metabolic (dysfunction)-associated fatty liver disease has been suggested as a more appropriate overarching term [2].

In either case, the spectrum of the disease is broad. The mildest type of the disease is simple steatosis, with at least 5% steatosis in the liver. If liver damage continues, inflammation can occur, and nonalcoholic steatohepatitis (NASH) may develop. This disease can progress to different degrees of fibrosis and eventually progress to cirrhosis or even hepatocellular carcinoma. Nevertheless, this sequence is not always linear, as hepatocellular carcinoma can arise from simple steatosis or from NASH without the development of previous fibrosis or cirrhosis (Fig. 1) [1].

The prevalence of NAFLD is approximately 25% of the general population. It is estimated that by 2030, the percentage of patients with NASH and F2 fibrosis will increase by 48%, those with F3 fibrosis by 88%, and those with cirrhosis by 118%. This will place it among the first or second most prevalent liver aetiologies for hepatocellular carcinoma [3].

Two major phenotypes can be described: the metabolic phenotype, which is the most predominant, and the immune-mediated phenotype. The main risk factors for the metabolic phenotype are female sex, being aged older than 60 years, a body mass index $\geq 30 \text{ kg/m}^2$, diabetes mellitus, hypertension and dyslipidaemia, among others. The risk of developing NASH, fibrosis or cirrhosis increases as more risk factors are combined [4]. The immune-mediated phenotype includes celiac disease, inflammatory bowel disease, systemic lupus erythematosus, rheumatoid arthritis, psoriasis and hidradenitis suppurativa. In the presence of any of these immune-mediated diseases, a smaller metabolic burden or fewer metabolic risk factors are necessary to trigger NAFLD, even in its more advanced stages. Moreover, as immune-mediated disease becomes more active or less controlled, liver disease develops in parallel [5].

The prevalence of NAFLD-associated cirrhosis has increased significantly in recent years. There were 2.5-fold and 2-fold increases in the prevalence of NASH cirrhosis and NAFLD-associated advanced fibrosis, respectively, in 2009–2012 compared to 1999–2002 in the USA [6]. This may be due not only to the increase in metabolic risk factors but also to the increasing focus on cirrhosis of unknown origin (cryptogenic cirrhosis) and its classification as NAFLD. Likewise, the prevalence of NAFLD-associated hepatocellular carcinoma has also increased significantly over time. From 2000 to 2010, the prevalence of hepatocellular carcinoma increased in patients with NAFLD by 21.5%; in 2010, NAFLD-associated hepatocellular carcinoma accounted for 35% of all cases [7].

Although the condition of NAFLD has been recognised for a long time, it was not until very recently that fat deposition in the liver was considered to cause problems. Moreover, unlike hepatitis, NAFLD is a noncontagious and nonstigmatising disease, thus it has not received adequate attention. To highlight the need for accurate diagnosis to initiate early treatment, this article describes the most appropriate methods of diagnosis and the therapeutic alternatives currently available.

2 Extrahepatic Manifestations of NAFLD

Nonalcoholic fatty liver disease may produce some extrahepatic effects. The most important are increased cardiovascular risk and renal involvement. A study evaluated different forms of subclinical atherosclerosis and found that patients with NAFLD had a markedly greater carotid intima-media thickness than healthy control subjects. Moreover, carotid intima-media thickness was higher in patients with NASH than in those with simple steatosis. In addition, carotid intima-media thickness was strongly associated with the degree of hepatic steatosis, necroinflammation and fibrosis among patients with NAFLD [8]. Another study reported that advanced fibrosis was positively associated with carotid intima-media thickness, the presence of carotid plaque and arterial stiffness in patients with NAFLD, independent of conventional cardiometabolic risk factors and insulin resistance [9]. The prevalence of chronic and end-stage renal disease is higher in patients with NAFLD than in healthy controls. In addition, as liver fibrosis progresses, the glomerular filtration rate decreases [10].

One of the most prominent extrahepatic manifestations of NAFLD is the development of oncologic processes. Although hepatocellular carcinoma is the tumour most frequently associated with NAFLD (hazard ratio = 16.73, $p = 0.008$), the risk of colon cancer in men (hazard ratio = 2.01, $p = 0.02$) and breast cancer in women (hazard ratio = 1.92, $p = 0.01$) also increases in patients with NAFLD [11].

Metabolic alterations are not only the cause of liver disease but can also arise as a consequence of it. In a study performed in patients with NASH but without baseline metabolic abnormalities (dyslipidaemia, hypertriglyceridemia, arterial hypertension and diabetes mellitus), it was
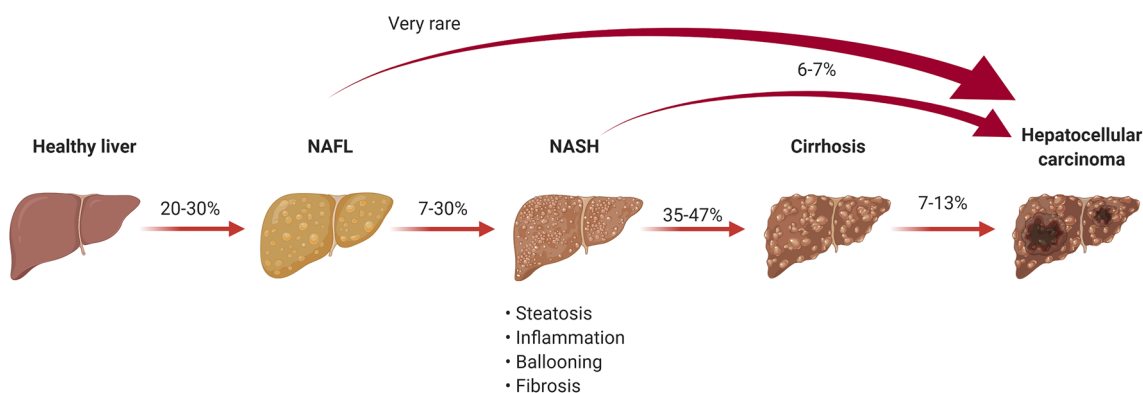

Fig. 1 Nonalcoholic fatty liver disease (NAFLD) spectrum. *NAFL* nonalcoholic fatty liver, *NASH* nonalcoholic steatohepatitis

found that after 5 years of follow-up, at some point, these patients developed some type of metabolic alterations. Patients with NAFLD and significant fibrosis were at risk of developing type 2 diabetes and arterial hypertension. In addition, the risk of metabolic abnormalities in patients with significant fibrosis was increased in the presence of obesity [12]. Therefore, it is necessary to monitor patients closely to detect these metabolic alterations not only at the time of diagnosis of liver disease but also at their onset.

Patients with NAFLD, especially those with stage F2 or F3 fibrosis, have an increased risk of all-cause mortality and hepatic-specific mortality. When patients do not have liver cirrhosis, the main causes of death are vascular events and extrahepatic tumours. When cirrhosis is present, the leading causes of death are hepatic decompensation and hepatocellular carcinoma [13].

The prevalence of NAFLD-related hepatocellular carcinoma has been increasing in recent years. The main risk factors in this group of patients are male sex, advanced age and diabetes [14]. As previously mentioned, this type of cancer can originate without prior fibrosis or cirrhosis. The proportion of patients with hepatocellular carcinoma without cirrhosis was 34.6% in patients with NAFLD. These percentages are in contrast with the proportion of patients with hepatocellular carcinoma without cirrhosis who have hepatitis C (8.9%) or hepatitis B (7.7%) or abuse alcohol (11.1%) [15].

3 Non-invasive Diagnosis of Hepatic Steatosis and Liver Fibrosis

Although increased transaminase serum/blood levels, especially alanine aminotransferase and aspartate aminotransferase, suggest liver damage, only 25–40% of patients with liver steatosis have elevated levels of these enzymes [16].

For this reason, normal transaminase levels should not rule out NAFLD in a patient with risk factors.

Biochemical scores and imaging techniques can be used for the noninvasive diagnosis of hepatic steatosis (Table 1). The most commonly used biochemical scores are the hepatic steatosis index or the fatty liver index [17, 18]. Both indices use variables that can be obtained routinely, such as the patient's age, sex, weight and height, body mass index, abdominal perimeter or transaminase levels. Through a formula using these data, each score provides a value that can predict the risk of developing hepatic steatosis. Table 2 shows the formula and the cut-off point for both indices.

Regarding imaging techniques used for the diagnosis of hepatic steatosis, ultrasonography, controlled attenuation parameter and magnetic resonance imaging-proton density fat fraction are the most important [19–21]. Ultrasonography has a specificity of 90–95% but a sensitivity of 60–70% when fat infiltration in the liver is less than 30%, which can lead to misdiagnosis [19]. Controlled attenuation parameter is read by software incorporated into FibroScan® that calculates the attenuation of the ultrasound signal; this is an easy and fast method that provides a numerical value that correlates with the histological degree of steatosis [20]. The accuracy of ultrasonography for hepatic steatosis assessment is affected by the severity of fibrosis [22], while controlled attenuation parameter is accurate in grading fatty infiltration, and the values are not influenced by liver fibrosis [23]. Magnetic resonance imaging-proton density fat fraction allows differentiation between the different degrees of hepatic steatosis much better than ultrasonography or controlled attenuation parameter. It is the most accurate method, but it is not available in many hospitals [21]. Currently, the development of noninvasive methods to detect NASH, including biochemical tests and imaging, is a challenge because they have suboptimal accuracy or they are patented prototypes that show limitations in clinical practice.

Table 1 Non-invasive methods to diagnose NAFLD

Hepatic steatosis	Biochemical tests	Hepatic steatosis index
		Fatty liver index
	Imaging techniques	Ultrasonography
		Controlled attenuation parameter
		Magnetic resonance imaging-proton density fat fraction
Steatohepatitis	Currently, there are no non-invasive methods of diagnosis implemented in clinical practice	
Hepatic fibrosis	Biochemical tests	NAFLD fibrosis score
		FIB-4
		Hepamet fibrosis score
	Imaging techniques	Transient elastography
		Magnetic resonance elastography

NAFLD nonalcoholic fatty liver disease, *FIB-4* Fibrosis-4

Like hepatic steatosis, hepatic fibrosis can be diagnosed by biochemical tests and imaging techniques (Table 1). The most commonly used biochemical tests are the NAFLD fibrosis score, FIB-4 index and Hepamet fibrosis score [24, 25]. The first two indices have been in use for more than 10 years and have very well-defined cut-off points, which should be corrected in patients aged older than 65 years because of the risk of false-positive results. These indices have a discrimination ability of 0.75 and 0.80 [24, 25]. The Hepamet fibrosis score is a scale developed specifically for liver fibrosis by the Spanish Association for the Study of the Liver (AEEH, Asociación Española para el Estudio del Hígado), and the discrimination ability of this index is significantly higher than the NAFLD fibrosis score and FIB-4 index (AUROC 0.85). All these scores have demonstrated a good ability to predict liver-related outcomes [26].

Two imaging methods are primarily used in the diagnosis of liver fibrosis: transient elastography and magnetic resonance elastography. Transient elastography is commonly used to detect other liver entities, such as hepatitis C, although the cut-off points used for the diagnosis of F3 liver fibrosis or cirrhosis are higher (approximately 13 and 16 kPa, respectively). However, patients with metabolic NAFLD have a high body mass index, and failure of this procedure with a medium probe begins at a BMI of 30 kg/m^2 (6.9% failure). The failure rate continues to increase at a BMI of 35–40 kg/m^2 (19% failure) and 40 kg/m^2 (59% failure). In the latter case, the failure rate is reduced to 4.9% using an XL probe. However, the use of an XL probe provides lower values, which may ultimately affect the diagnosis [27]. However, and as was the case for hepatic steatosis diagnosis, magnetic resonance elastography is a more accurate test. However, it is not available in all centres, and its complexity hinders its everyday use in clinical practice [28]. Both transient and magnetic resonance-based elastography have been associated with poor outcomes in individuals with NAFLD [29, 30].

4 NAFLD Treatment

The first therapeutic strategy to consider in the treatment of NAFLD is lifestyle intervention. Patients with metabolic NAFLD walk less, are more sedentary and have less sedentary-to-active transitions than healthy subjects. The recommended physical exercise for these patients is aerobic or even resistance (anaerobic) exercise for those with reduced mobility. Although both types of exercise are comparable in terms of hepatic improvement, aerobic exercise also improves cardiopulmonary function [31].

If the patient is overweight or obese, a hypocaloric diet should be recommended. In the case of a normal-weight patient who is not expected to lose weight, the diet should preferably be low in fat; above all, saturated fatty acids should be reduced. If the dietary pattern is Mediterranean (fruit, fish, vegetables, nuts, olive oil), the intrahepatic lipid content will improve more than with a low-fat diet, and insulin sensitivity will improve [32].

In addition to the type of diet, food preparation also plays an important role. It is known that red meat and processed meat increase the risk of metabolic NAFLD. Fried or overcooked meat at high temperatures for a long time produces heterocyclic amines that can lead to higher oxidative stress and inflammation, which will further worsen liver conditions [33]. However, nutraceuticals such as coffee have demonstrated a potential role in the management of NAFLD [34].

There are currently no drugs specifically approved for the treatment of NAFLD, although pioglitazone and vitamin E are endorsed by societies in biopsy-proven NASH [35]. However, several marketed drugs could change their indication. Glucagon-like peptide type 1 receptor agonists are commonly used for the management of diabetes, but some clinical trials have been conducted using liraglutide and semaglutide for the treatment of NASH [36, 37]. Both drugs were shown to resolve NASH (39% with liraglutide and 60% with semaglutide) in patients with or without

Table 2 Formula and cut-off points for biochemical scores to diagnose NAFLD

Hepatic steatosis index (HSI)

Formula: 8 × (ALT/AST) ratio + BMI + 2 (if diabetes mellitus) + 2 (if female)

Interpretation:
 HSI < 30 → no NAFLD
 HSI > 36 → NAFLD

Fatty liver index (FLI)

Formula: 100/(1 + EXP((1) × (0.953 × Ln(triglycerides)) + (0.139 × BMI) + (0.718 × Ln(GGT)) + (0.053 × (waist circumference)) − 15.475))

Interpretation:
 FLI < 30 → no NAFLD
 FLI > 60 → NAFLD

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *BMI* body mass index, *GGT* gamma-glutamyl transferase, *NAFLD* nonalcoholic fatty liver disease

diabetes. However, although both medications improved NASH, neither was able to improve liver fibrosis, which is the main prognostic determinant of patients with metabolic NAFLD [36, 37].

Given the pathophysiological characteristics of this disease, anti-inflammatory, antifibrotic and metabolic drugs are needed. To date, obeticholic acid is the only drug approved for a different indication (primary biliary cholangitis) that has shown positive results in improving liver fibrosis in patients with NASH in a phase III trial [38], while other drugs such as lanifibranor (a peroxisome proliferator-activated receptor agonist) have showed promising results for NASH [39].

5 Conclusions

Nonalcoholic fatty liver disease is a disorder with high morbidity and mortality that should be properly diagnosed to establish an appropriate treatment. Although hepatic steatosis may be present, it can be difficult to identify. Hence, any metabolic or immune-mediated risk factors should be considered. The main prognostic determinant of this disease is liver fibrosis. Serum/blood levels of liver enzymes are not a good indicator of liver damage and should not be used to guide decisions in clinical practice. Thus, noninvasive methods based on biochemical parameters should be used as a first step in the evaluation of any patient in whom this disease is suspected. Currently, in the absence of available drugs, the most relevant intervention is lifestyle modification.

Declarations

Conflict of interest The author reports no conflict of interest.

Ethics approval This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by the author.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material Not applicable.

Code availability Not applicable.

Authors' contributions The author meets the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, takes responsibility for the integrity of the work as a whole and has given his approval for this version to be published.

References

1. Mahady SE, Adams LA. Burden of non-alcoholic fatty liver disease in Australia. J Gastroenterol Hepatol. 2018;33(Suppl. 1):1–11. https://doi.org/10.1111/jgh.14270.
2. Eslam M, Sanyal AJ, George J, International Consensus P. MAFLD: a consensus-driven proposed nomenclature for metabolic associated fatty liver disease. Gastroenterology. 2020;158(7):1999-2014 e1. https://doi.org/10.1053/j.gastro.2019.11.312.
3. Estes C, Anstee QM, Arias-Loste MT, Bantel H, Bellentani S, Caballería J, et al. Modeling NAFLD disease burden in China, France, Germany, Italy, Japan, Spain, United Kingdom, and United States for the period 2016–2030. J Hepatol. 2018;69(4):896–904. https://doi.org/10.1016/j.jhep.2018.05.036.
4. Ampuero J, Aller R, Gallego-Durán R, Banales JM, Crespo J, García-Monzón C, et al. The effects of metabolic status on nonalcoholic fatty liver disease-related outcomes, beyond the presence of obesity. Aliment Pharmacol Ther. 2018;48(11–12):1260–70. https://doi.org/10.1111/apt.15015.
5. Tovoli F, Negrini G, Fari R, Guidetti E, Faggiano C, Napoli L, et al. Increased risk of nonalcoholic fatty liver disease in patients with coeliac disease on a gluten-free diet: beyond traditional metabolic factors. Aliment Pharmacol Ther. 2018;48(5):538–46. https://doi.org/10.1111/apt.14910.
6. Kabbany MN, Conjeevaram Selvakumar PK, Watt K, López R, Akras Z, Zein N, et al. Prevalence of nonalcoholic steatohepatitis-associated cirrhosis in the United States: an analysis of national health and nutrition examination survey data. Am J Gastroenterol. 2017;112(4):581–7. https://doi.org/10.1038/ajg.2017.5.
7. Dyson J, Jaques B, Chattopadyhay D, Lochan R, Graham J, Das D, et al. Hepatocellular cancer: the impact of obesity, type 2 diabetes and a multidisciplinary team. J Hepatol. 2014;60(1):110–7. https://doi.org/10.1016/j.jhep.2013.08.011.
8. Targher G, Bertolini L, Padovani R, Rodella S, Zoppini G, Zenari L, et al. Relations between carotid artery wall thickness and liver histology in subjects with nonalcoholic fatty liver disease. Diabetes Care. 2006;29(6):1325–30. https://doi.org/10.2337/dc06-0135.
9. Chen Y, Xu M, Wang T, Sun J, Sun W, Xu B, et al. Advanced fibrosis associates with atherosclerosis in subjects with nonalcoholic

fatty liver disease. Atherosclerosis. 2015;241(1):145–50. https://doi.org/10.1016/j.atherosclerosis.2015.05.002.

10. Adams LA, Anstee QM, Tilg H, Targher G. Non-alcoholic fatty liver disease and its relationship with cardiovascular disease and other extrahepatic diseases. Gut. 2017;66(6):1138–53. https://doi.org/10.1136/gutjnl-2017-313884.

11. Kim GA, Lee HC, Kim MJ. Reply to: "The role of NAFLD in extrahepatic malignancies: the importance of ruling out the effect of obesity." J Hepatol. 2018;68(5):1094–5. https://doi.org/10.1016/j.jhep.2018.01.007.

12. Ampuero J, Aller R, Gallego-Durán R, Crespo J, Calleja JL, García-Monzón C, et al. Significant fibrosis predicts new-onset diabetes mellitus and arterial hypertension in patients with NASH. J Hepatol. 2020;73(1):17–25. https://doi.org/10.1016/j.jhep.2020.02.028.

13. Vilar-Gómez E, Calzadilla-Bertot L, Wai-Sun Wong V, Castellanos M, Aller-de la Fuente R, Metwally M, et al. Fibrosis severity as a determinant of cause-specific mortality in patients with advanced nonalcoholic fatty liver disease: a multi-national cohort study. Gastroenterology. 2018;155(2):443-57.e17. https://doi.org/10.1053/j.gastro.2018.04.034.

14. Younossi Z, Stepanova M, Ong JP, Jacobson IM, Bugianesi E, Duseja A, et al. Nonalcoholic steatohepatitis is the fastest growing cause of hepatocellular carcinoma in liver transplant candidates. Clin Gastroenterol Hepatol. 2019;17(4):748-55.e3. https://doi.org/10.1016/j.cgh.2018.05.057.

15. Mittal S, El-Serag HB, Sada YH, Kanwal F, Duan Z, Temple S, et al. Hepatocellular carcinoma in the absence of cirrhosis in United States veterans is associated with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol. 2016;14(1):124-31.e1. https://doi.org/10.1016/j.cgh.2015.07.019.

16. Blais P, Husain N, Kramer JR, Kowalkowski M, El-Serag H, Kanwal F. Nonalcoholic fatty liver disease is underrecognized in the primary care setting. Am J Gastroenterol. 2015;110(1):10–4. https://doi.org/10.1038/ajg.2014.134.

17. Lee JH, Kim D, Kim HJ, Lee CH, Yang JI, Kim W, et al. Hepatic steatosis index: a simple screening tool reflecting nonalcoholic fatty liver disease. Dig Liver Dis. 2010;42(7):503–8. https://doi.org/10.1016/j.dld.2009.08.002.

18. Bedogni G, Bellentani S, Miglioli L, Masutti F, Passalacqua M, Castiglione A, et al. The fatty liver index: a simple and accurate predictor of hepatic steatosis in the general population. BMC Gastroenterol. 2006;6:33. https://doi.org/10.1186/1471-230X-6-33.

19. Loomba R. Role of imaging-based biomarkers in NAFLD: recent advances in clinical application and future research directions. J Hepatol. 2018;68(2):296–304. https://doi.org/10.1016/j.jhep.2017.11.028.

20. Karlas T, Petroff D, Sasso M, Fan JG, Mi YQ, de Ledinghen V, et al. Individual patient data meta-analysis of controlled attenuation parameter (CAP) technology for assessing steatosis. J Hepatol. 2017;66(5):1022–30. https://doi.org/10.1016/j.jhep.2016.12.022.

21. Caussy C, Reeder SB, Sirlin CB, Loomba R. Noninvasive, quantitative assessment of liver fat by MRI-PDFF as an endpoint in NASH trials. Hepatology. 2018;68(2):763–72. https://doi.org/10.1002/hep.29797.

22. Zhang B, Ding F, Chen T, Xia LH, Qian J, Lv GY. Ultrasound hepatic/renal ratio and hepatic attenuation rate for quantifying liver fat content. World J Gastroenterol. 2014;20(47):17985–92. https://doi.org/10.3748/wjg.v20.i47.17985.

23. de Lédinghen V, Vergniol J, Foucher J, Merrouche W, le Bail B. Non-invasive diagnosis of liver steatosis using controlled attenuation parameter (CAP) and transient elastography. Liver Int. 2012;32(6):911–8. https://doi.org/10.1111/j.1478-3231.2012.02820.x.

24. Ampuero J, Pais R, Aller R, Gallego-Durán R, Crespo J, García-Monzón C, et al. Development and validation of hepamet fibrosis scoring system-a simple, noninvasive test to identify patients with nonalcoholic fatty liver disease with advanced fibrosis. Clin Gastroenterol Hepatol. 2020;18(1):216-25.e5. https://doi.org/10.1016/j.cgh.2019.05.051.

25. Anstee QM, Lawitz EJ, Alkhouri N, Wong VW, Romero-Gómez M, Okanoue T, et al. Noninvasive tests accurately identify advanced fibrosis due to NASH: baseline data from the STELLAR trials. Hepatology. 2019;70(5):1521–30. https://doi.org/10.1002/hep.30842.

26. Younes R, Caviglia GP, Govaere O, Rosso C, Armandi A, Sanavia T, et al. Long-term outcomes and predictive ability of non-invasive scoring systems in patients with non-alcoholic fatty liver disease. J Hepatol. 2021;75(4):786–94. https://doi.org/10.1016/j.jhep.2021.05.008.

27. Myers RP, Pomier-Layrargues G, Kirsch R, Pollett A, Duarte-Rojo A, Wong D, et al. Feasibility and diagnostic performance of the FibroScan XL probe for liver stiffness measurement in overweight and obese patients. Hepatology. 2012;55(1):199–208. https://doi.org/10.1002/hep.24624.

28. Hsu C, Caussy C, Imajo K, Chen J, Singh S, Kaulback K, et al. Magnetic resonance vs transient elastography analysis of patients with nonalcoholic fatty liver disease: a systematic review and pooled analysis of individual participants. Clin Gastroenterol Hepatol. 2019;17(4):630-7.e8. https://doi.org/10.1016/j.cgh.2018.05.059.

29. Boursier J, Hagstrom H, Ekstedt M, Moreau C, Bonacci M, Cure S, et al. Non-invasive tests accurately stratify patients with NAFLD based on their risk of liver-related events. J Hepatol. 2022. https://doi.org/10.1016/j.jhep.2021.12.031.

30. Han MAT, Vipani A, Noureddin N, Ramirez K, Gornbein J, Saouaf R, et al. MR elastography-based liver fibrosis correlates with liver events in nonalcoholic fatty liver patients: a multicenter study. Liver Int. 2020;40(9):2242–51. https://doi.org/10.1111/liv.14593.

31. Hashida R, Kawaguchi T, Bekki M, Omoto M, Matsuse H, Nago T, et al. Aerobic vs. resistance exercise in non-alcoholic fatty liver disease: a systematic review. J Hepatol. 2017;66(1):142–52. https://doi.org/10.1016/j.jhep.2016.08.023.

32. Gepner Y, Shelef I, Komy O, Cohen N, Schwarzfuchs D, Bril N, et al. The beneficial effects of Mediterranean diet over low-fat diet may be mediated by decreasing hepatic fat content. J Hepatol. 2019;71(2):379–88. https://doi.org/10.1016/j.jhep.2019.04.013.

33. Zelber-Sagi S, Ivancovsky-Wajcman D, Fliss Isakov N, Webb M, Orenstein D, Shibolet O, et al. High red and processed meat consumption is associated with non-alcoholic fatty liver disease and insulin resistance. J Hepatol. 2018;68(6):1239–46. https://doi.org/10.1016/j.jhep.2018.01.015.

34. Ebadi M, Ip S, Bhanji RA, Montano-Loza AJ. Effect of coffee consumption on non-alcoholic fatty liver disease incidence, prevalence and risk of significant liver fibrosis: systematic review with meta-analysis of observational studies. Nutrients. 2021;13(9):3042. https://doi.org/10.3390/nu13093042.

35. European Association for the Study of the Liver, European Association for the Study of Diabetes, European Association for the Study of Obesity. EASL-EASD-EASO clinical practice guidelines for the management of non-alcoholic fatty liver disease. J Hepatol. 2016;64(6):1388–402. https://doi.org/10.1016/j.jhep.2015.11.004.

36. Armstrong MJ, Gaunt P, Aithal GP, Barton D, Hull D, Parker R, et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. Lancet. 2016;387(10019):679–90. https://doi.org/10.1016/S0140-6736(15)00803-X.

37. Newsome PN, Buchholtz K, Cusi K, Linder M, Okanoue T, Ratziu V, et al. A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. N Engl J Med. 2021;384(12):1113–24. https://doi.org/10.1056/NEJMoa2028395.

38. Younossi ZM, Ratziu V, Loomba R, Rinella M, Anstee QM, Goodman Z, et al. Obeticholic acid for the treatment of non-alcoholic steatohepatitis: interim analysis from a multicentre, randomised, placebo-controlled phase 3 trial. Lancet. 2019;394(10215):2184–96. https://doi.org/10.1016/S0140-6736(19)33041-7.

39. Francque SM, Bedossa P, Ratziu V, Anstee QM, Bugianesi E, Sanyal AJ, et al. A randomized, controlled trial of the pan-PPAR agonist lanifibranor in NASH. N Engl J Med. 2021;385(17):1547–58. https://doi.org/10.1056/NEJMoa2036205.