Clinical Practice Guidelines

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# EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease☆

European Association for the Study of the Liver (EASL)*, European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO)



## Introduction

The Clinical Practice Guidelines propose recommendations for the diagnosis, treatment and follow-up of non-alcoholic fatty liver disease (NAFLD) patients and are the product of a joint effort by the European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO). They update a position statement based on the 2009 EASL Special Conference [1].

The data have been retrieved by an extensive PubMed search up to April 2015. The final statements are graded according to the level of evidence and strength of recommendation, which are adjustable to local regulations and/or team capacities (Table 1) [2]. In particular, screening for NAFLD in the population at risk should be in the context of the available resources, considering the burden for the national health care systems and the currently limited effective treatments. The document is intended both for practical use and for advancing the research and knowledge of NAFLD in adults, with specific reference to paediatric NAFLD whenever necessary. The final purpose is to improve patient care and awareness of the importance of NAFLD, and to assist stakeholders in the decision-making process by providing evidence-based data, which also takes into consideration the burden of clinical management for the healthcare system.

## Definition

NAFLD is characterised by excessive hepatic fat accumulation, associated with insulin resistance (IR), and defined by the presence of steatosis in >5% of hepatocytes according to histological analysis or by a proton density fat fraction (providing a rough estimation of the volume fraction of fatty material in the liver) >5.6% assessed by proton magnetic resonance spectroscopy ($^1$H-MRS) or quantitative fat/water selective magnetic resonance imaging (MRI). NAFLD includes two pathologically distinct conditions with different prognoses: non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH); the latter covers a wide spectrum of disease severity, including fibrosis, cirrhosis and hepatocellular carcinoma (HCC) (Table 2).

The diagnosis of NAFLD requires the exclusion of both secondary causes and of a daily alcohol consumption $\geqslant$30 g for men and $\geqslant$20 g for women [1]. Alcohol consumption above these limits indicates alcoholic liver disease. The relationship between alcohol and liver injury depends on several cofactors (type of alcoholic beverage, drinking patterns, duration of exposure, individual/genetic susceptibility), rendering simple quantitative thresholds at least partly arbitrary. Specifically, patients consuming moderate amounts of alcohol may be still predisposed to NAFLD if they have metabolic risk factors. Of note, the overall impact of metabolic risk factors on the occurrence of steatosis appears to be higher than that of alcohol in these patients [3]. The definitive diagnosis of NASH requires a liver biopsy.

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These Guidelines were developed by the EASL, EASD and the EASO, and are published simultaneously in the *Journal of Hepatology*, *Diabetologia* and *Obesity Facts*.

*Abbreviations:* ALT, alanine transaminase; BMI, body mass index; CAP, controlled attenuation parameter; CCR, chemokine receptor; CK-18, cytokeratin-18 fragments; CKD, chronic kidney disease; CT, computed tomography; CVD, cardiovascular disease; EASD, European Association for the Study of Diabetes; EASL, European Association for the Study of the Liver; EASO, European Association for the Study of Obesity; ELF, enhanced liver fibrosis; F, fibrosis stage; FIB-4, fibrosis 4 calculator; FLI, fatty liver index; HbA1c, glycosylated haemoglobin A1c; HCC, hepatocellular carcinoma; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; IFG, impaired fasting glucose; IR, Insulin resistance; LDL, low-density lipoprotein; MetS, metabolic syndrome; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NAFL, non-alcoholic fatty liver; NAFLD, non-alcoholic fatty liver disease; NFS, NAFLD fibrosis score; NAS, NAFLD Activity Score; NASH, non-alcoholic steatohepatitis; NPV, negative predictive value; OGTT, oral glucose tolerance test; PNHS, paediatric NAFLD histological score; PNPLA3, patatin-like phospholipase domain containing 3; PPAR, peroxisome proliferator-activated receptor; PPV, positive predictive value; PUFA, polyunsaturated fatty acids; RCT, randomized controlled trials; SAF, steatosis, activity and fibrosis; T2DM, type 2 diabetes mellitus; TM6SF2, transmembrane 6 superfamily 2; UDCA, ursodeoxycholic acid; US, ultrasound.

**Table 1. Evidence grade used for the EASL–EASD–EASO Clinical Practice Guidelines on NAFLD** (adapted from the GRADE system [8]).

| Grading of evidence | Notes | Symbol |
|---|---|---|
| High quality | Further research is very unlikely to change our confidence in the estimate effect | A |
| Moderate quality | Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate effect | B |
| Low or very low quality | Further research is very likely to have an important impact on our confidence in the estimate of effect and may change the estimate effect. Any estimate of effect is uncertain | C |
| **Grading of recommendations** | **Notes** | **Symbol** |
| Strong recommendation warranted | Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost | 1 |
| Weaker recommendation | Variability in preferences and values, or more uncertainty: more likely a weak recommendation is warranted Recommendation is made with less certainty; higher cost or resource consumption | 2 |

**Table 2. The spectrum of NAFLD and concurrent diseases.**

| Disease | Subclassification | Most common concurrent diseases |
|---|---|---|
| NAFLD* | NAFL<br>• Pure steatosis<br>• Steatosis and mild lobular inflammation<br>NASH<br>• Early NASH: no or mild (F0-F1) fibrosis<br>• Fibrotic NASH: significant (≥F2) or advanced (≥F3, bridging) fibrosis<br>• NASH-Cirrhosis (F4)<br>Hepatocellular carcinoma^ | ° AFLD-Alcoholic fatty liver disease<br>° Drug-induced fatty liver disease<br>° Hepatitis C virus-associated fatty liver (genotype 3)<br>° Others<br>• Haemochromatosis<br>• Autoimmune hepatitis<br>• Coeliac disease<br>• Wilson's disease<br>• A/hypo-betalipoproteinaemia lipoatrophy<br>• Hypopituitarism, hypothyroidism<br>• Starvation, parenteral nutrition<br>• Inborn errors of metabolism (Wolman disease [lysosomal acid lipase deficiency]) |

* Also called Primary NAFLD and associated with metabolic risk factors/components of Metabolic Syndrome:

1. Waist circumference ⩾94/⩾80 cm for Europid men/women.
2. Arterial pressure ⩾130/85 mmHg or treated for hypertension.
3. Fasting glucose ⩾100 mg/dl (5.6 mmol/L) or treated for T2DM.
4. Serum triacylglycerols >150 mg/dl (>1.7 mmol/L).
5. HDL cholesterol <40/50 mg/dl for men/women (<1.0/<1.3 mmol/L).

°Also called secondary NAFLD. Note that primary and secondary NAFLD may coexist in individual patients. Also NAFLD and AFLD may coexist in subjects with metabolic risk factors and drinking habits above safe limits.

^Can occur in the absence of cirrhosis and histological evidence of NASH, but with metabolic risk factors suggestive of "burned-out" NASH.

*Recommendations*

- Patients with IR and/or metabolic risk factors (i.e. obesity or metabolic syndrome [MetS]) should undergo diagnostic procedures for the diagnosis of NAFLD, which relies onthe demonstration of excessive liver fat (**A1**)
- Individuals with steatosis should be screened for secondary causes of NAFLD, including a careful assessment of alcohol intake. The interaction between moderate amounts of alcohol and metabolic factors in fatty liver should always be considered (**A1**)
- Other chronic liver diseases that may coexist with NAFLD should be identified as this might result in more severe liver injury (**B1**)



## Prevalence and incidence

NAFLD is the most common liver disorder in Western countries, affecting 17–46% of adults, with differences according to the diagnostic method, age, sex and ethnicity [4]. It parallels the prevalence of MetS and its components, which also increases the risk of more advanced disease, both in adults and in children. NAFLD is also present in 7% of normal-weight (lean) persons [5], more frequently in females, at a younger age and with normal liver enzymes. Their liver disease may nonetheless be progressive [6].

NAFLD incidence has rarely been measured. It was 20-86/1000 person-years based on elevated liver enzymes and/or on ultrasound (US), and 34/1000 per year by $^{1}$H-MRS [7].

The need for NAFLD screening in the community has been questioned given the high direct and indirect costs of testing, the low predictive value of non-invasive tests, the risks of liver biopsy and the lack of effective treatments [8]. However, the progressive form of NAFLD (i.e. NASH), particularly when associated with advanced fibrosis, should be identified in patients at risk (age >50 years, type 2 diabetes mellitus [T2DM] or MetS), because of its prognostic implications. Validated cost utility studies on extensive screening programmes are eagerly awaited. Similarly, although familial clustering occurs, family screening is not generally advisable, with the exception of cases with defined inherited diseases (e.g. lysosomal acid lipase deficiency).

*Recommendations*

- All individuals with steatosis should be screened for features of MetS, independent of liver enzymes. All individuals with persistently abnormal liver enzymes should be screened for NAFLD, because NAFLD is the main reason for unexpectedly elevated liver enzymes (**A1**)
- In subjects with obesity or MetS, screening for NAFLD by liver enzymes and/or ultrasound should be part of routine work-up. In high risk individuals (age >50 years, T2DM, MetS) case finding of advanced disease (i.e. NASH with fibrosis) is advisable (**A2**)